DECADE OF DISCOVERY

Advances In Cancer Research 1971-1981

U.S. DEPARTMENT OF
HEALTH AND
HUMAN SERVICES
Public Health Service
National Institutes of Health

Oncogenes

by Jeffrey L. Fox

"In 1981 and 1982, there was more progress in cancer research than during most of the preceding decade," declares Robert C. Gallo, tumor virologist, and a recent winner of the Lasker Award for basic research in medicine. That progress sometimes seems like a "speeding truck that outruns its headlights," adds a colleague at the National Cancer Institute, George Vande Woude, who explains that research is moving so quickly and with such momentum that scientists doing it often can't guess just what they'll discover next.

Other scientists working in this field echo the excitement and optimism. It is "the coming of another dawn," suggests J. Michael Bishop of the University of California, San Francisco, and also a recipient of the 1982 Lasker Award. "After centuries of bewilderment, the human intellect has finally laid hold of the cancer cell with a grip that may eventually extract the deadly secrets of the disease," he says. This tight grip is letting scientists take a close and penetrating look at cancer cells, a look that they hope will provide a better understanding of this disease.

"Will we be able to parlay these revelations into a strategy for the control of cancer?" Bishop asks. No one can answer that question with any certainty. But there is a growing conviction among many scientists that these new insights about cancer will lead the way toward better methods of preventing and treating this disease.

What recent findings underpin this new optimism? "Tumor viruses have revealed to us a set of human genes whose activities may lie in the heart of every cancer, no matter what its cause," Bishop points out. "The enemy has been found. It is part of us, and we have begun to understand the lines of its attack."

This "enemy" Bishop refers to is a set of genes, often called oncogenes because of their association with cancer cells and with certain viruses that cause cancer in animals. Although first identified in viruses, these genes have counterparts that have since been found in almost every animal cell, healthy or otherwise, that's been looked at. No one knows for sure just what these genes do normally. Some of them are thought to be activated only during special periods, such as when an embryo is developing. But what has caught the attention of scientists is evidence that these genes are either inappropriately activated or mutated in cancer cells, and may be responsible for causing disease. How these genes become active when they ought not to be is puzzling. Scientists speculate that various agents, including chemicals and certain viruses, may trigger the genes to cause cancer in the cells that happen to receive those "environmental" insults.

No one yet can say how any of these genes--either the ones from cells or from viruses--act at a biochemical level to disrupt normal cell behavior. But it is considered a great stride forward to have identified only a small number that have this potential to cause cancer from the more than 50,000 genes that occur in each cell. And with the powerful tool of recombinant DNA technology, those 15 or 20 genes can be isolated and studied as molecular entities. Scientists are confident that the unsolved biochemical issues will be solved. Meanwhile, a great deal is being learned about the genes themselves and how even very slight changes in some of them will trigger cancer.

Those changes can be of at least two kinds. In some instances, a single chemical change in a gene, causing a small change in the protein produced by that gene, is apparently enough to make a cell become cancerous. In other cases, the change involves abnormal rearrangements of large amounts of genetic material. This important change seems to affect how active a particular gene

becomes in a cell and, presumably, how much of the gene's protein product is made.

Human cells contain 23 pairs of chromosomes, the gene-carrying structures in all cells that have a distinct nucleus. Sometimes chromosomes break. And although the cell is usually able to repair such breaks, occasionally a part of one chromosome may be exchanged permanently with part of another. This event, called a chromosomal translocation, involves the moving around of large segments of chromosomes, each containing hundreds of genes.

What happens to the cell as a result is much like what happens when you dial a wrong telephone number. For example, if you intend to dial 555-5911, but dial the last three digits, 911, first, by mistake, you will get an operator for the police and fire departments. In many cities in the U.S., 911 is a "distress call." That's a far cry from reaching your intended party. In a similar way, a "translocation" of otherwise correct information in a cell's chromosome can drastically change the message.

Patients with certain cancers almost always have chromosomal translocations in their cancer cells. By itself, this is not a new finding. For example, more than 10 years ago, Lore Zech of the Karolinska Institute in Stockholm discovered a characteristic translocation in which parts of two specific chromosomes shift places in cancer cells of almost all patients with Burkitt's lymphoma. According to Janet D. Rowley, a cell geneticist and professor of medicine at the University of Chicago, "What's excited everyone now is the new finding that some of these translocations include certain oncogenes."

Burkitt's lymphoma arises in cells of the lymphatic system that make antibodies. These substances help the body's immune system recognize foreign invaders. Gallo, in collaboration with Carlo Croce of the Wistar Institute in

Philadelphia, showed that the translocation moves an oncogene onto the same chromosome as the genes that produce antibodies. This moving of oncogenes next to activated genes is thought to be enough to trigger the changes that make these cells cancerous.

This same abnormal pattern now has been found in an entirely different animal, the mouse. Because nearly the same thing occurs in such different species, scientists believe the chromosomal translocation is not accidental.

Geneticist Philip Leder of Harvard Medical School and his colleagues there and at NCI were studying a cancer of the antibody-producing cells in mice. These cancer cells secrete copious amounts of antibody molecules. In the mouse cancer cells, as in the human Burkitt's cells, one of a particular pair of chromosomes carrying a gene needed to produce antibodies was rearranged. A gene that did not resemble any of the known antibody genes was involved, according to Ilan R. Kirsch of NCI, one of Leder's collaborators. "Eventually, we were able to identify that gene," he recalls. It was an oncogene.

Thus, that illicit gene "partnership" suddenly seemed to make sense, in terms of explaining the cells' abnormal condition: the simplest explanation is that putting the oncogene into this new position somehow deregulates it. The result is a cancer cell. This notion was made at least as early as 1981 by Swedish tumor biologist George Klein of the Karolinska Institute in Stockholm, and was suspected by investigators studying human oncogenes. Now, the idea is gaining strong support from results coming out of many laboratories.

In fact, similar findings, in which chromosomal translocations involve the movement of oncogenes, are coming out of studies of several human cancers, including acute myelogenous and chronic myelogenous leukemias.

"The basic mechanism is clear--a translocation," says Croce, one of several scientists studying this phenomenon. Although he admits: "I don't know what causes a translocation--it may be an accident or it may be induced by viruses or by some other agent," he adds, "I don't think translocation is the answer. It's one of the answers. There are probably several steps that occur."

For example, these oncogenes might be triggered by chemicals that can change the activity of genes and possibly turn them on. Still other insults may trigger genes, including the placement of "enhancer regions" near oncogenes to turn them on when they shouldn't be. Enhancer regions are poorly understood parts of genes that seem to activate other neighboring genes.

It's still "difficult to understand what all of this means," says University of Chicago's Rowley. "Bits of data conflict; some we just don't have; some we don't understand. For example, what are these genes doing in normal cells? And what do translocations do to influence gene activity?" She concludes: "It's still the era of the black box."

And yet there's a firm, widespread conviction among many cancer researchers, including Rowley, that the "black box" soon may be pried open.

Some other recent developments may represent a glimpse into the mysteries enclosed in that box. Those developments involve the close scrutiny of slight changes occurring in particular oncogenes to cause cancer. Think again about the dialing and misdialing of a telephone number. Before, otherwise correct numbers were "translocated." Now, consider a simpler error but one with equally dramatic results. This time you substitute a single digit in a long string of numbers. For example, you intend to dial a number in part of Georgia having area code 912, but by mistake you dial 911. Depending on where you are calling from, this mistake again signals "distress," and you are connected to

an emergency operator. Something like this mistake, which appears minor, may be all that's needed to cause cancer in some cells.

The discovery that some human cancers could be caused by such minor changes in a single cellular gene was made public late in 1982 by scientists from several institutions, including Robert A. Weinberg at the Massachusetts Institute of Technology and the affiliated Whitehead Institute for Biomedical Research in Cambridge; Mariano Barbacid at the National Cancer Institute in Bethesda, Maryland; and Michael Wigler at Cold Spring Harbor Laboratory on Long Island in New York.

The initial research revolved around genes from human bladder, lung and colon cancer cells. Subsequently, such genes have been found in a variety of different cancers. The research depends on an assay that is based on observing growth patterns of certain mouse cells, called NIH 3T3 cells. These cells are unique: they can be "fed" genes from other sources, such as from human or mouse cancer cells. The 3T3 cells take up the gene and make the protein it codes for.

Left more or less alone, 3T3 cells usually will grow in an orderly fashion in laboratory dishes. But when fed oncogenes, the cells will undergo typical shape, behavioral, and biochemical changes associated with becoming cancerous. When cells altered in this way are introduced into healthy mice, they cause tumors in the animals.

Using this cancer gene assay, several labs have been searching through the inventory of genes from human tumors, looking for those that can cause dramatic changes in 3T3 cells. Such a gene was isolated from human bladder cancer cells and compared to its counterpart that occurs in normal cells.

How do the two versions of the same gene differ? The surprising answer came last year, according to molecular biologist Weinberg. The two forms of

the gene differed by a single chemical alteration that causes a slight change in one protein in the cells to somehow make them cancerous, he says. Though relatively minor, such changes can significantly affect the function of proteins. For example, a simple exchange of one of the 534 amino acids in the protein hemoglobin causes sickle-cell anemia. However, almost nothing is known about how a single amino acid change in one protein of a cell can make it become cancerous.

The original observations with bladder cancer have been extended to include cells from other patients with cancers of the bladder and also of other tissues. Geoffrey M. Cooper from the Dana Farber Cancer Institute in Boston and his collaborators, for instance, have looked at samples from more than a dozen different tissues and they consistently find differences between the proteins from cancerous samples and those from normal samples. "Whether that can be generalized remains to be seen," he says.

Cooper and others believe that at least two steps are needed to trigger cancer and that the 3T3 mouse cells already have taken the first one. Cooper says: "The transforming genes we detect in the 3T3 assay are probably active during the late stages of cancer causation. The genes that are picked up this way probably trigger the final step in transformation." Stopping this final step by attacking the oncogene product may be enough to prevent cancer. So it may be possible now to exploit these new findings while continuing to study the full implications of the molecular changes.

Will these recent findings ever fit into a coherent explanation of cancer? "It's not as simple as you'd like," answers NCI's Gallo. "There are already 17 such genes," he says, referring to the growing collection of known oncogenes, only four of which have been implicated in any way in the causation of human cancer. "There could be from 20 to 30," he continues. "But apparently

the number of genes are quite limited, and we now have a handle on them. There will be multiple ways for enhancing their expression, for modifying them, and for triggering them."

Along with many other scientists who formerly hoped they would find simple answers for how cancer takes hold of seemingly normal cells, Gallo now says, "It may be more complicated than a simple, single pathway."

The proteins specified by these genes so far have greatly frustrated the scientists studying them. Although some of the proteins have been identified, their function remains elusive. "The next step will be to understand what these proteins are doing," Gallo says. Our next insights will come by studying these molecules and understanding what they do in cells. "Progress may be slow," he warns. But he and many of his colleagues are increasingly confident that progress will be made.

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Foreword

Henry C. Pitot, M.D., Ph.D.
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The National Cancer Act, the landmark legislation that greatly expanded and intensified this nation's effort to conquer cancer, will be 10 years old December 23, 1981. The National Cancer Advisory Board, a Presidentially appointed body charged with advising and assisting the Federal anticancer effort, is publishing this volume to document the progress made possible by that Act during the past decade, and to remind the American people that much remains to be done before this disease is totally controlled.

The National Panel of Consultants on the Conquest of Cancer, whose 1970 report to the Senate formed the basis of the Act, predicted correctly that no single, miraculous breakthrough would occur. The panel also was correct in its forecast that heightened effort in the 1970s would lead to progressive improvements in our ability to prevent and treat cancer.

It is not possible to describe in this report every advance of the past decade. We have chosen instead to look at the broader changes and gains that already are benefitting people; the achievement of cures for some forms of cancer, the gains in survival for many forms of cancer, an enhanced knowledge of how to prevent some types of it, and the sweeping advances in fundamental research that in decades to come will serve as the basis for further improvements in prevention, diagnosis, treatment and the continuing care needed by many patients.

The progress we describe is the fruit of many decades of research, but the National Cancer Act of 1971 increased the yield to such a degree that for cancer, the 1970s became an unparalleled decade of discovery. Funds appropriated by Congress for the National Cancer Institute rose from $230 million in 1971 to $1 billion in 1980.

At the same time, the cancer legislation made provisions for the National Cancer Institute to establish and expand mechanisms that permitted a coordinated, intensive approach to the cancer problem. Chief among these provisions are those that formed the comprehensive cancer centers, and training and education programs to move validated research results swiftly to the public and into everyday medical practice.

Comprehensive cancer centers, of which there were three before 1971, multiplied across the country. Now there are 20. In each center, teams of experts work together on problems of research, teaching and patient care—the very sort of multidisciplinary effort that is needed to solve the cancer problem.

Centers also coordinate regional programs, disseminate information to the public, and bring new information to clinics, hospitals and physicians. Community cancer centers and programs developed widely at the local level in the past decade and now provide an important structure for the work of doctors who specialize in cancer. Much of the progress of the 1970s was made possible by centers, and by the expansion of cancer research in virtually every academic medical center, and in many independent laboratories and profit making organizations.

Expanded training programs, supported by the Institute in medical schools and universities, increased the number of scientists devoted to research in cancer. Training programs also enhanced cancer care at the community level, largely by increasing the number of doctors who are cancer specialists.

As one example, there were barely 100 medical oncologists practicing in the

United States in the late 1960s. By 1980 there were about 2,800 physicians specializing in medical oncology, and more than 1,800 of these were certified specialists.

Improved cancer survival rates, and decreases in cancer deaths for patients under age 45, occurred in part because of the community-based oncologists who see many cancer patients themselves, and extend their expertise by consulting with general practitioners who treat still other patients.

Other special efforts launched in the 1970s included a major construction program to build or renovate cancer research facilities throughout the United States; task forces to organize research efforts against cancers of the breast, large bowel, prostate, bladder, and pancreas; and many projects to move research findings into the hands of the public and of those who could use the findings to prevent or treat cancer. The Institute entered cooperative arrangements with many other nations so that advances, no matter where made, could be applied against cancer throughout the world.

The substantial progress in the 1970s is a testimonial to the tenacious efforts of many individuals and organizations in the public and private sectors, and to the tax support and private gifts of Americans. Congress, the several Presidents, the National Cancer Institute and other Federal agencies, the American Cancer Society and other nonprofit organizations and their volunteers, many unnamed individuals, and the medical and research communities worked together to bring about these enormous achievements.

Ten years ago, there were some individuals who expected that our achievements would be even greater, hoping that by now the means to prevent or cure all forms of cancer would be at hand. Those who have devoted themselves to the cancer problem are deeply disappointed that this is not the case. But men and women studying cancer knew in 1971, and reaffirm now, that the conquest of cancer will be a long-term effort. Much remains to be done.

Treatment advances have been great; we now can cure most patients with some types of cancer, and some patients with most types of cancer. However we are just part way to our ultimate treatment goal to cure all who develop the disease. Efficient tools and tests must be found to detect and diagnose cancer when it is in its earliest stages. Even when curative, treatments need to be refined to eliminate or reduce side effects. Until all patients can be cured, we must develop better methods of continuing and terminal care for those who are not. And as research advances help more and more patients to live longer or be cured, more attention must be given to the psychosocial and physical problems of those who have been afflicted with the disease.

In the area of prevention, efforts in the 1970s set the stage for much to be done in the decades ahead. We must develop better, faster and cheaper ways to identify environmental substances and lifestyle habits that cause cancer. Without these, our nation will not be able to cope with the increasing number of chemicals in our environment, and individuals will not have the information they need to adjust their personal habits to eliminate or reduce risks of cancer.

If we are to improve our ability to detect potential carcinogens, we must learn to

combine effective laboratory tests for the cancer-causing potential of chemicals, with large-scale studies of population groups to identify factors that protect against cancer or increase risk.

A major research problem is to determine how exposures to many cancer hazards—a fact of life in modern society—affect risk for individuals. We need also to learn more about how the body deals with hazardous exposures, and to develop ways to help the body resist cancerous changes at the cellular level when such exposures occur. The developing field of chemoprevention may provide substantial payoff here, and will be of major research interest in years to come.

Fundamental research in cancer biology forms the underpinnings for all other research programs within the National Cancer Program because it seeks to define the properties of cancer cells that distinguish them from normal, healthy cells and to identify critical steps in the cancer process.

Within the past several years, new technologies—all discussed in this document—have opened seemingly limitless opportunities for the study of cancer cells. The new technologies are recombinant DNA technology, and hybridoma technology.

Using these exciting new tools and others that surely will be developed, there is hope that we will be able to solve the fundamental mysteries of the cancer process. The knowledge and understanding that come from basic research in the years ahead will allow scientists to exploit differences between cancerous and normal cells for treating, detecting and preventing the disease.

Spurred on by the momentum we now have, we all can look forward to another decade of progress toward the conquest of cancer.

Henry C. Pitot, M.D., Ph.D.

During the 1970s we witnessed two heartening trends toward improved survival rates emerging from research on treatment for the more than 100 forms of cancer. The first, exemplified by the story on childhood cancer, resulted from fine-tuning the successful experimental therapies of the 1960s. With vigorous clinical effort, survival of children with cancer steadily increased from a near hopeless rate of less than 10 percent to over 50 percent. By 1980 many of these former cancer patients were adults. They were surviving free of disease, having children of their own, working and leading normal, productive lives. This is the definition of cure and the goal of all cancer treatment.

The second trend followed a changed approach toward the treatment of cancers that predominantly affect adults and is illustrated by our story on breast cancer. The approach arose from new insights on ways cancer cells function and spread. Cancer is often present throughout the body even though it can be found only in a localized tumor. Treating the total disease by using anticancer drugs right from the start, in addition to surgery, has prolonged survival for women with breast cancer. In the coming decade, it is hoped this strategy will extend the lives of patients with other forms of cancer, such as cancer of the colon, rectum, pancreas and lung.

I.

Increasing Survival For Patients

Increasing Survival For Patients

CHILDHOOD CANCERS: A BRIGHTENING PICTURE

Jennette Hubbard Hall — Jennie—is 35, lives with her husband Larry and their four children in suburban Fremont, California, down the bay from Oakland. The children, two of them adopted, are ages 16, 12, 10 and 8. The household includes a female goat and her kid, a pig, a female cat and a varying population of kittens, one old dog and one young dog, a mixed flock of full-sized hens and bantams, and a rooster.

Jennie helps Larry in his concrete contracting and construction business. She keeps track of

children and animals. She runs family errands, using either the mini-car or a pickup truck. She plans to return to college. She fights against overweight. Jennie's very active life may seem typical for many women. But one thing is not typical. Twenty-one years ago, with medical odds against her, Jennette Hubbard developed and survived childhood leukemia.

In March 1959, 13-year-old Jennie was diagnosed by her family physician as having acute lymphocytic leukemia (ALL). He referred her to the care of Dr. Denman Hammond at the University of Southern California -affiliated Children's Hospital of Los Angeles. Dr. Hammond and the hospital were well known for their work with childhood cancers; yet hospital studies of that period indicated Jennie had only one chance in a hundred to live for 5 years. Today, a young leukemia patient's chances for 5-year survival are 50 percent —one chance in two — and still improving.

Not only were the odds a devastating 99 percent against surviving, at that time there was no Candlelighters Foundation or specially-trained hospital staff to offer support to cancer patients and their parents. There was, in fact, a sign on the waiting room wall in the outpatient clinic at Children's Hospital that read, "Parents are requested not to talk to each other."

Jennie's parents do not speak easily about the period. They did not see how her ordeal would be made easier if she knew she had cancer, so they did not tell her until she was in college and beginning to date. "It was the philosophy then to protect the child," her mother explains, simply and without apology. "I know the thinking has changed, but I don't know if we'd do it differently today." They told Jennie she had anemia, the same as an aunt, and that she would have to be treated for it the rest of her life.

The parents walked a fine line—supporting their daughter through colds, pneumonia, and blood transfusions. They combatted the side effects of chemotherapy — nausea, fatigue, weepiness, hair loss, excruciating mouth sores, weight gain and skin problems. Through it all they maintained the protective shield they had raised, keeping the secret of cancer from Jennie.

Dr. Kenneth Williams, facing page, of L.A. Children's Hospital has seen encouraging progress in treatment of childhood cancer. One of his first patients in 1960 was Jennette Hubbard, then 14 and under treatment for acute lymphocytic leukemia. Children with ALL had little chance of surviving. Those who did well on chemotherapy were in medical limbo — physicians didn't know whether to keep them on drugs indefinitely or take them off and risk relapse. It was doubtful those who lived would be able to bear children. Now half of all children with ALL are cured. Jennie is shown at left and with husband Larry Hall, bottom. Today parents, patients and siblings turn to groups such as the Candlelighters for emotional support, practical advice. This Las Vegas, Nevada, group, below, is one of more than 100 nationwide.

Once Jennie came home from school with the exciting news that all the students in biology class were going to examine their blood under a microscope. The Hubbards called her teacher; Jennie mustn't know her blood was different.

In her kitchen nearly 20 years later, Jennie recalls what happened. "I kept saying my blood was orange, which it was (probably due to the chemotherapy). The teacher kept saying, 'Jennie, why do you always want to call attention to yourself? Your slide looks just like everyone else's'."

Perhaps she didn't want to know. A girl friend spent a whole day trying to convince Jennie that she had leukemia. Jennie replied, "If it were true, my dad would have told me."

Jennie also remembers a neighbor boy who tried to tell her. "He was one of those kids who was always messing around with a chemistry set in his garage. Who would believe someone like that?" Then she remembers an aunt who was dying of breast cancer. "She said to me, 'I always thought you would go before I did.' It didn't make sense to me."

Jennie was treated entirely on an outpatient basis under one of the early protocols of the NCI-supported Children's Cancer Study Group. Her treatment — methotrexate, 6-mercaptopurine and prednisone—was administered by her family physician under Children's Hospital supervision. She and her parents drove monthly to Los Angeles for checkups. "We tried to make each visit special," Mrs. Hubbard recalls. "After all, we were coming to Hollywood."

On the other hand, they tried not to spoil Jennie. "The doctors impressed upon us that it was important to keep life as normal as possible," Mrs. Hubbard remem-

More Cures, Followup for Childhood Cancers

"At last, we are beginning to see the fruits of research on childhood cancers," declares Dr. Giulio D'Angio, director of the cancer center at Children's Hospital of Philadelphia. "Now more than half of children with a variety of cancers can expect to live a normal life free of disease."

These advances began in the 1950s with the use of surgery and radiation therapy and have continued with addition of chemotherapy—cancer fighting drugs. For example, by 1960 doctors had learned that with surgery and radiation they could cure 40 percent of children with Wilms' tumor, a rare cancer of the kidney that usually occurs in infancy. Since then the National Wilms' Tumor Study Group (physicians who jointly plan treatment and share results for any Wilms' tumor patients referred to them) has added a blend of anticancer drugs to surgery and radiation for a treatment plan that cures 90 percent of their patients.

Children with cancers of the bone and connective tissue, such as Ewing's sarcoma and rhabdomyosarcoma, once were cured only 10 to 20 percent of the time. But physicians working at cancer centers and in cooperative groups, such as the Children's Cancer Study Group directed by Dr. Denman Hammond in Los Angeles, showed that surgery followed by local radiation of the cancer, followed in turn by chemotherapy to halt distant spread of cancer cells, can cure 60 to 70 percent of children.

Despite the successes, work still remains to find better therapies for the 50 percent of children who are not cured. Of particular concern are two forms of childhood cancers in which survival rates remain poor; brain cancer and metastatic neuroblastoma (a nerve cell cancer that occurs most often in the adrenal gland and spreads to distant parts of the body). Neither radiation, drugs nor combinations of the two have had an important effect on survival. Fresh approaches are needed.

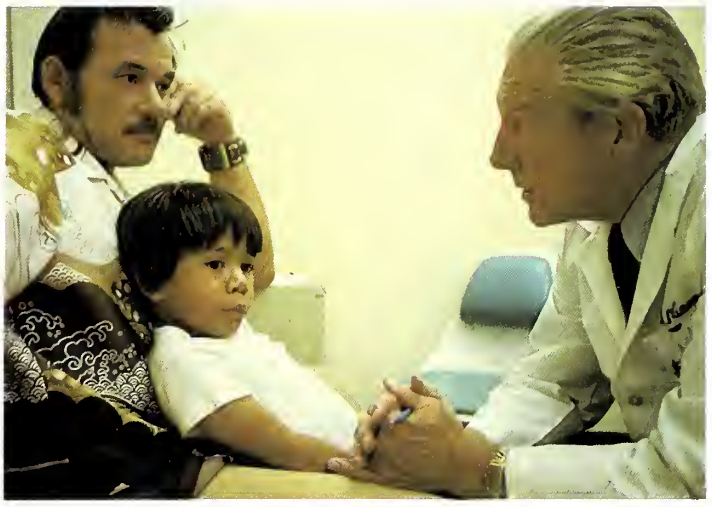
In addition, the treatments that work may need fine-tuning. "Cure has its tomorrows," warns Dr. D'Angio. "As we have more survivors, we will have more complications—ones we may not see for many years." To find them as soon as possible, the National Cancer Institute supports record-keeping by groups like D'Angio's so physicians may be alerted to any possible late effects in cured children.

For example, a small percentage of children who had radiation to the brain have shown some decrease in IQ and a scattering of learning disabilities. But serious consequences have been few.

Cancer seems to leave the children with few psychological scars. A followup study of long-term survivors treated at St. Jude Children's Research Hospital in Memphis suggests they have few serious problems getting along normally in society.

It was long believed drug treatment might interfere with parenthood. Yet a significant number of former childhood cancer patients have gone on to have children of their own. A study of over 100 pregnancies in which one parent had been treated as a child for cancer showed no greater rate of birth defects or spontaneous abortions than for the general population.

Physicians now are trying to minimize treatment to limit side effects without sacrificing any of the survival gains of the 1970s. This work highlights one of the important trends of the 1980s.



Jennie Hall, treated in an early study, was cured of leukemia. She married and had children, left, two of whom are adopted. At right, Marc Gulla, age 6 and in remission for 2 years, participates in a current leukemia study that attempts to prevent recurrences without overtreating children who should do well. His father Peter and L.A. Children's Hospital's Dr. Williams discuss results of biopsy of child's testicles — hiding place along with brain for leukemia cells that drugs miss. Report was negative. Patients with positive biopsy get radiation to testicles and second complete round of drug treatment.

bers, "not to run to Disneyland or celebrate Christmas early." Jennie went to school if she was able, even when she would not have the energy to stay the whole day.

"My one concession to her, and I recommend it for anyone with a chronically sick child, was a redwood chaise longue that we bought and put in the living room. She could lie down or sit up; it was adjustable, moveable and comfortable."

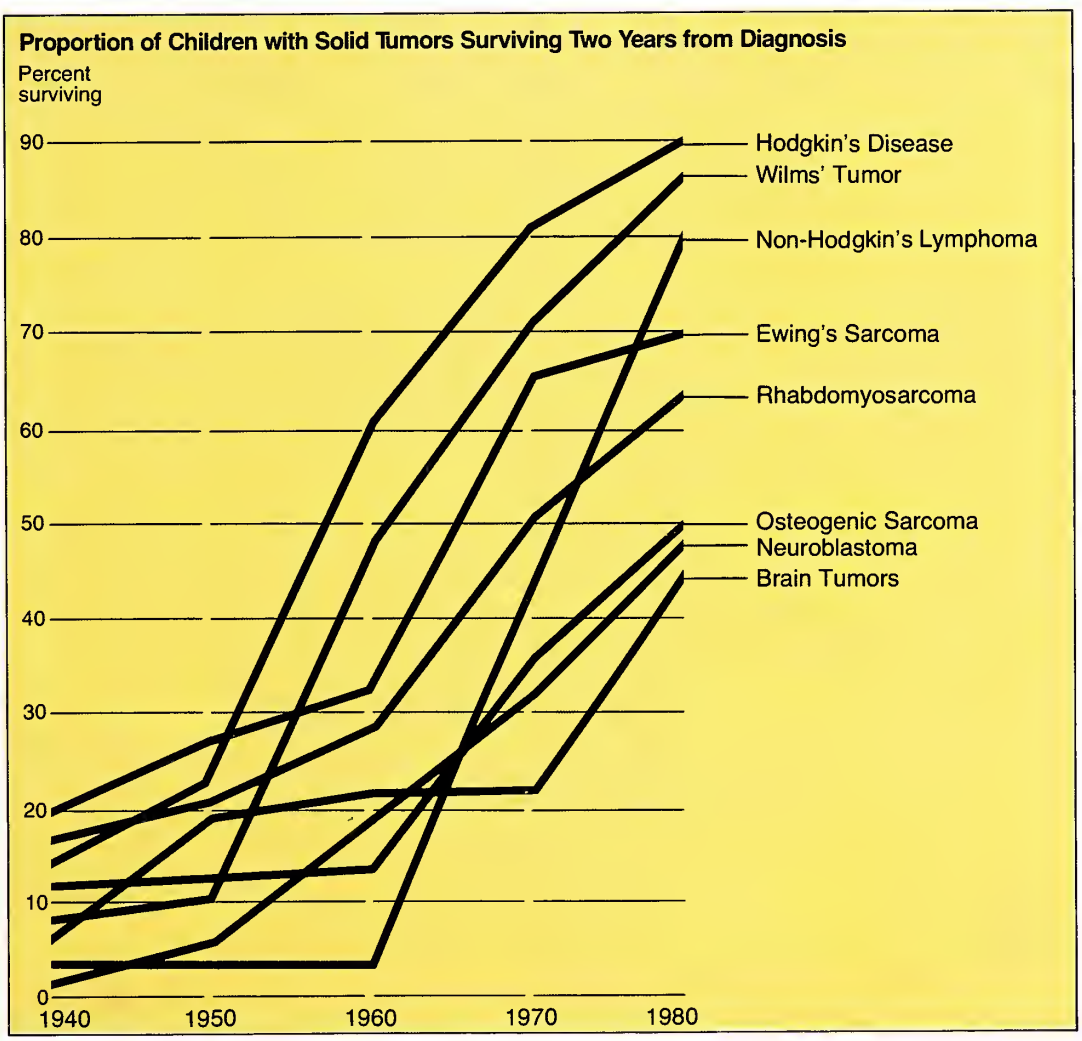
It was also a source of envy among the other Hubbard children. Everyone wanted to lie on the chaise longue but when Jennie wanted it, she always got it.

Mr. and Mrs. Hubbard spent a few quiet moments each morning in their garden, praying that they were doing the right thing and that for just that one day they would continue to make the right decisions. But it was never easy.

"Sometimes," Mrs. Hubbard remembers, "I prayed that 10 years would have passed. I knew Jennie would be gone, and I believed we would be over our grief." She looks at her husband and her face brightens. "Ten years later, Jennie *was* gone —married to Larry and expecting Ellen."

Jennie told Larry about the leukemia several months after they began dating. "We had dated for a summer before the relationship became serious. I'd heard his mother say a number of times that Larry was crazy about kids and ought to have a big family. I was sure I'd never be able to

Physicians combine skills in surgery, radiation, and chemotherapy to deliver maximum effect against solid tumors. Increasing numbers of children are now being cured, "normal life span" replaces "long-term survival" as goal of treatment. Even stubborn tumors yield individual successes, miracles of human tenacity. Now 9, Jennifer Dale, left and below, survived massive abdominal surgery at age 3 for neuroblastoma, a form of cancer that occurs in the nerve cells of the adrenal gland. Her parents faced harrowing decisions, financial strains that pushed limits of previously idyllic marriage. Jennie is disease-free, active, slated for acceleration in school.



While picture brightens for increasing number of children with cancer, stubborn forms of disease resist all but most daring treatment. Dana Lesher, right and below with parents and sister, failed standard leukemia treatment. Experimental therapy bought time for parents and physician to opt for bone marrow transplant with sister, Suzanne, as donor. Transplant worked, but there are side effects. Research now enables physicians to pinpoint such high risk patients at diagnosis and tailor treatment accordingly.

have children," Jennie explains.

How did he react? "I went home and read everything I could find on leukemia," Larry recalls. "I was never going to call Jennie again. I didn't want to go out with a girl who was going to die." Three weeks later he phoned her.

Jennie remained on chemotherapy more than 7 years. Currently, children being treated for leukemia take drugs for 2 or 3 years after the disease is in remission. "We didn't know what would happen, frankly, if we took her off," recalls Dr. Kenneth Williams. A colleague of Dr. Hammond's, he oversaw Jennie's periodic return visits to Children's Hospital for checkups.

"We had a few studies indicating how well long-term survivors were doing on treatment, but we had so few children no longer taking drugs who were alive and doing well," Dr. Williams explains. "Jennie and Larry finally made the decision to stop treatment themselves." Fifteen years later he still shakes his head in disbelief.

Jennie explains. "Larry questioned whether I was still sick, or whether it was the medicine that was making me sick." She consistently suffered from the side effects of the drugs, including mood changes that left her crying all day. "I really was fed up with the hassle of the drug reactions. I don't think we thought about the possibility that I could die."

Jennie and Larry discussed with Dr. Williams their impending marriage, and Jennie told him she had stopped her chemotherapy. Her health has been so good since then that she occasionally has had trouble convincing Fremont physicians that she ever had leukemia.

Since Jennie's bout with leukemia, clinical studies at centers throughout the country have defined principles for treating this most common form of childhood cancer. Now children receive a combination of drugs until they go into remission. On the average this takes 4 weeks. They then receive one or more combinations of drugs to kill any surviving cancer cells. Today, all chemotherapy is stopped after 2 to 3 years.

By the late 1950s enough progress had been made so that some children were going into remissions that lasted 2 to 3 years. But physicians observed children, whose leukemia apparently had been wiped out, relapsed with spread of leukemia to the brain. The protective mechanism called the blood-brain barrier was preventing anticancer drugs from entering the delicate tissues of the brain, creating a haven for leukemic cells.

Clinical studies initiated by Dr. Donald Pinkel at St. Jude Children's Hospital in Memphis in the 1960s and at other centers in the early 1970s explored the concept of attacking these hidden cells early in the course of treatment. They used radiation to the brain and injections of drugs directly into the cerebrospinal fluid as part of the initial therapy. This treatment, called CNS prophylaxis, has become standard. It is a

critical step in treating ALL.

Still, research remains to be done to reduce side effects in the children who are cured and to find ways to further benefit the 50 percent who are not cured by standard therapy. One step was made during the 1970s with the identification of at least four forms of ALL. Certain features—such as the number of white blood cells at the time the leukemia is diagnosed, the child's age and sex, and markers on the surface of the leukemia cells — distinguish the type of ALL that is most common and most responsive to combinations of drugs and CNS prophylaxis. Research continues for better therapies to use against other forms of ALL.

Dana Lesher had a form of ALL that does not respond to standard therapy. Dana developed leukemia when she was 3. Now 10, she is in long-term remission, but her apparent victory has been dearly bought. Dana suffers from a condition known as graft versus host (GVH) disease, caused by a bone marrow transplant, performed when the technique was still highly experimental. Only the prospect of certain death without an attempt made the risk worth the try.

In a GVH reaction, the healthy new bone marrow rejects the tissue of the patient. GVH reaction is not uncommon, one reason why bone marrow transplants are done only as a last resort. Chronic GVH disease such as Dana's, however, is rare. Her skin has thickened and tightened around her muscles, and much of her "play" is actually physical therapy to try to maintain some suppleness of the skin. Her doctor does not know whether the GVH may worsen or whether it is stabilized, but the transplant has saved her life. Standard treatment had failed and failed again. High dose chemotherapy, also experimental, fended off a relapse for over a year and then failed. Now, more than 3 years after bone marrow was taken from the hip of her sister Suzanne and injected into Dana's bloodstream, there has been no evidence of disease.

In addition to GVH disease, Dana has other side effects from the earlier treatments. "Those 18 months on the high-dose drug therapy had their side effects, it's true" Dana's mother Kay says matter-of-factly. "But they bought us time until bone marrow transplant was a possibility." Kay pauses. "If it weren't for cancer research, we would have lost Dana."

Dana's treatment began at an Armed Forces hospital where Kay Lesher learned the hard way the assertive, protective tactics that become routine to parents of cancer patients. "The hospital was bureaucratic, unattuned to the needs of 3-year old patients facing a potentially fatal disease.

"I remember one battle over naptime," Kay says. "Parents weren't supposed to stay in their children's rooms, but the hospital had provided no place for parents to sit, except in the hall. Dana cried and cried if I left her, but

both of us could nap if I stayed with her."

Defiant, Kay finally refused to leave the room. With the absolute certainty of regimentation, the nurse charged, "Mrs. Lesher, you can't do that. All the other mothers will want to stay, too."

"Good," said Kay. "Just send them all in."

But it was rarely that simple or that clear-cut. Kay and her husband Neal, now deputy commander of the range group at Nellis Air Force Base in Las Vegas, Nevada, had other growing children — Kathy, now 21, and Suzanne, now 19. When the Leshers switched Dana's treatment to the Los Angeles Children's Hospital, the change helped the older girls as well as Dana. They were able to travel to Los Angeles with their parents, to be with Dana in the hospital and to understand better what Dana was facing. Suzanne, who was going through a difficult adolescence, matured with the responsibility of being Dana's marrow donor.

Kenneth Williams, Jennie Hall's doctor, also supervised Dana's intermediate treatment. "I think he was getting her ready for the bone marrow transplant long before he began discussing it with us," Kay says. "I think he knew it was her only chance." He referred the Leshers to the University of California at Los Angeles hospital and Dr. Stephen Feig, who performed the transplant and has been Dana's oncologist since that time.

How did they survive that ordeal: Kay and Dana in one hospital isolation room for months; Neal traveling back and forth; friends taking brief turns with Dana so her parents could spend a few hours together?

"Dana never gave up, so we didn't either," her father says.

They deal with the enormity of battling their daughter's disease much as the Hubbards dealt with Jennie's; they face each day as it comes. Kay cites an old Asian proverb, "The only way to eat an elephant is one bite at a time."

Kay suggests parents need to know all the treatment options for their child consecutively before they begin any treatment. "You have to have A, B and C ready to go, because if A fails, you don't have time to do research on B and C."

When you first meet Dana, you see a bony child with dark glasses and scar tissue on her nearly translucent skin. When she begins to talk, all awareness of

Rescue Tactics for Bone Cancer

Osteogenic sarcoma primarily strikes teenagers. It is a form of cancer usually occurring in the long bones of the arm or leg, and standard therapy has been and still is amputation of the limb. Until recently almost everyone who got this disease died within 2 years because, even with surgery, cancer cells spread to the lung.

During the 1970s, physicians combined several advances in cancer diagnosis and treatment to increase the likelihood of curing this disease. Now as many as half of those whose cancer has not spread at the time of diagnosis are cured, and as many as 70 percent of all patients are still living 2 years after diagnosis. In the early part of the decade, physicians began trials of Adriamycin, a new anticancer antibiotic from Italy. It had activity against osteogenic sarcoma and 11 other forms of cancer. In the treatment of osteogenic sarcoma, Adriamycin usually is given immediately following surgery in an attempt to kill any cancer cells that already may have spread to the lungs.

When doctors found osteogenic sarcoma, a form of bone cancer, was the cause of his leg pain, Las Vegas teen Steve Berry, left, had his leg amputated above knee. Disease free and in college, he plays tennis (as well as guitar) but is still shy about dating. Jacques Washington, right, had osteogenic sarcoma in his upper left arm. In the past this meant loss of entire arm. Since cancer had not spread, surgeons performed a daring new procedure—implanting a thin metal rod in place of the cancerous bone—saving muscle and tendon and enabling Jacques to pick up and hold daughter, Random, with both arms, far right.

Cure has its tomorrows, says Dr. Giulio D'Angio, left, director of the cancer center at Children's Hospital of Philadelphia. Dr. D'Angio and group of physicians follow children cured of cancer to spot any late side effects. So far serious consequences have been few. Belief that drug treatment might interfere with parenthood has proven incorrect for most patients. At least one study shows no greater rate of birth defects or spontaneous abortions among former cancer patients. Goal now is to minimize treatment to limit side effects without sacrificing survival gains.

her physical problems disappears.

Dana's a charmer. As she speaks one hears a tiny adult. She's been the poster child for Nevada Easter Seals and is enthusiastic and articulate when asked about her star status.

"It's a lot of work, you know," she responds. "I had to meet the governor. I have to explain things to people and I went around to the stores to check on our canisters. I talked to people on television."

Kay explains that Dana is proud of the wheelchair the Easter Seals Society has given her. To Dana it is something she clearly earned in return for the work she has done for the society. Although she prefers a tricycle for getting around—it's good exercise for her muscles and sets her less apart—she is aware that the wheelchair is more appropriate for professional appearances.

Despite her handicaps, Dana is alert and seems full of energy, always ready for the next adventure or project or, most definitely, the next conversation.

If she seems mature in some ways, it is no wonder. Neal says her affiliation with Easter Seals "takes her out of herself and makes her think of others. It's been good for her."

Death is no stranger to this child. She and her parents have discussed it, both because Kay's mother died while Dana was in treatment and because it was something Dana needed to face for herself.

"I told her what I believe," Kay said, "that a person's spirit or energy just changes to a different form, that there is life after life. We've talked about it since," Kay says, "and she seems to have used that concept to develop a belief she's comfortable with."

In spite of the progress, Dana, Kay and Neal still must face the GVH disease as well as the other side effects. The Leshers declined a prestigious transfer to Brussels for Neal, an Air Force colonel, because the Belgian climate would have been too harsh for Dana. "We're dealing with the price tags now," Kay says.

One is struck that she says "dealing with," not "paying." For the Leshers there is no doubt that for Dana the benefits outweigh the costs of the struggle. "Her quality of life is still good," says Neal. "She enjoys life. She gets so much out of it." He pauses, his voice uncertain. "She gives so much, too...the influence these kids have on people around them. A friend of mine, facing surgery, told me he kept thinking to himself, 'If that little Dana can handle it, so can I!' "

Neal stops. The room is quiet. Dana is outside, playing with the other children in the gathering dusk.

Physicians also began using methotrexate, a drug inactive against osteogenic sarcoma at low doses, in a daring new way that allows them to administer extremely high doses. They found that an antidote, called citrovorum factor, literally rescues normal cells from destruction by the highly toxic large doses of methotrexate.

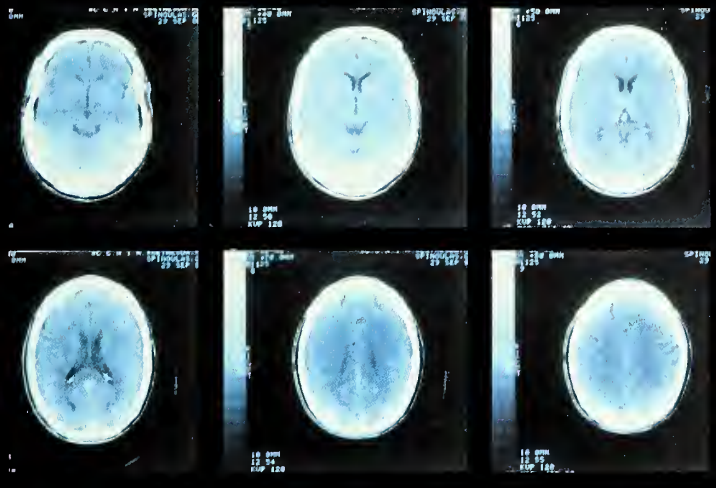
While oncologists were developing drug treatments, surgeons found that if they remove lung metastases as they develop, they can prolong survival of their patients. Surgical removal of lung metastases is now standard practice at many hospitals.

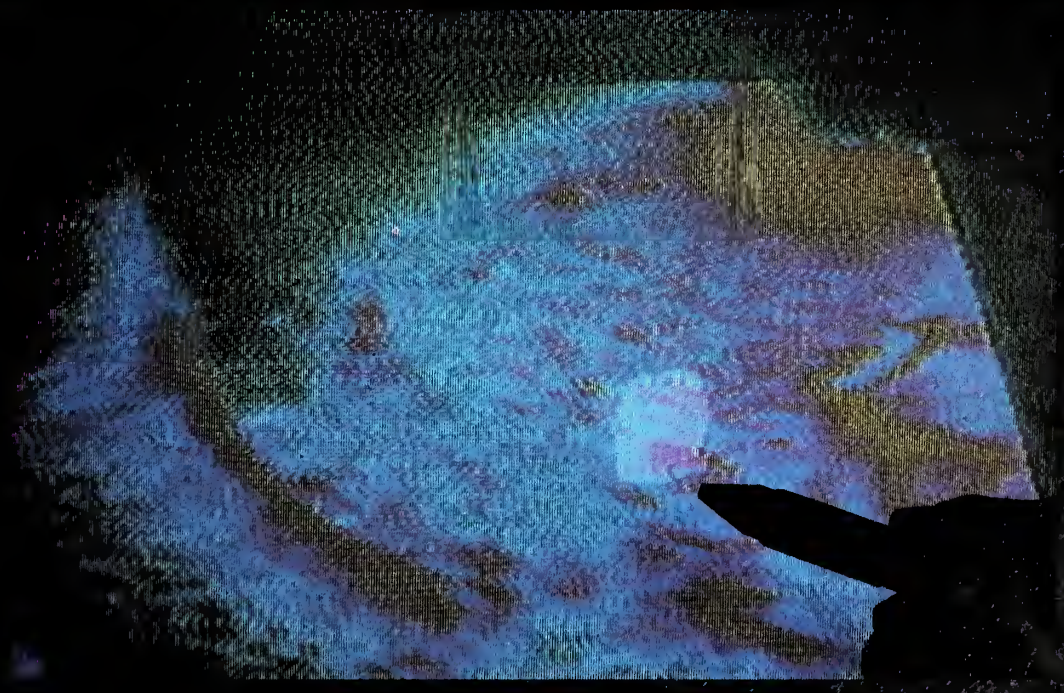
With full lung tomograms and computerized axial tomography (CAT), highly sophisticated diagnostic techniques introduced in the 1970s, physicians can find lung metastases much earlier than with conventional chest x-rays.

Some patients may be spared amputation through an alternative operation that preserves the limb. In some hospitals, osteogenic sarcoma patients may have cancerous bone replaced by a prosthesis, or artificial bone, made from the metal vitallium.

The exact contributions of earlier and better diagnosis, drug therapy and surgery remain to be defined. But whatever the reasons, the increased survival of osteogenic sarcoma patients is cause for encouragement.

An array of technology is used to help physicians locate cancers. Flexible optical fibers transmit high intensity light through endoscopes — long tubes, facing page, that tunnel into internal organs to explore surfaces. Small brushes and knives to take biopsies are remotely controlled by physician, left. Imaging devices send short bursts of sound into body. Echoes reflected from tissue are transformed on screen into colored outline of tissues and organs, bottom and lower center. The CAT (computer-assisted tomographic) scanner, first applied in the 1970s to x-ray the head, below, revolutionized detection of brain tumors. Expanded CAT system now scans entire body, upper center. It uses computers to organize thousands of x-rays, taken by rotating machine around patient.





Increasing Survival For Patients

BREAST CANCER: DRUGS MAKE A DIFFERENCE

Every year I live is critical for my childrens' growth and development. The stakes are too high for me not to take chances with experimental treatment."-- Barbara Chambers.

"Two weeks after I got out of the hospital, I was on a ladder holding one end of a ceiling beam helping my son remodel my kitchen." – Shirley Conard.

"I called the National Cancer Institute's toll-free information service. They sent me to the National Surgical Adjuvant Breast Project right here in Pittsburgh. I had a mastectomy, 30 x-ray treatments and chemotherapy. I missed only 10 days of work." --Ivona Kemp.

"I drive, clean my house, swim, bowl, do everything I did before." – Rita George.

"Sorry I have to cancel my interview. I've made it to the finals of a city-wide golf tournament." --Telephone message from woman with breast cancer.

These women seem super-

charged with life energy. All have breast cancer.

All have received potent anticancer drugs that, it is hoped, will enable them to live a normal lifetime, free of the devastating disease that among cancers is the greatest killer of women. During 1981, in the United States alone, breast cancer will take the lives of more than 37,000 women and will be discovered in about 110,000 women. One American woman in 11 will develop breast cancer.

Today drug treatment is used as a sequel to surgery or radiation as well as in cases of recurrence or metastasis (the spread of disease to other parts of the body). Drugs are beginning to boost survival rates that have been stuck at a plateau for 50 years. Although trends already are apparent, the statistics that reflect increased survival are expected to become more dramatic in the next 5 to 10 years.

The rationale for using drugs for breast cancer has evolved from a new concept of how this cancer spreads.

In 1894 Dr. William Halsted at Johns Hopkins Hospital pioneered the radical breast cancer surgery that bears his name. The operation included removal of the tumor along with the whole breast, the underlying muscle and the lymph glands that surround and drain the breast.

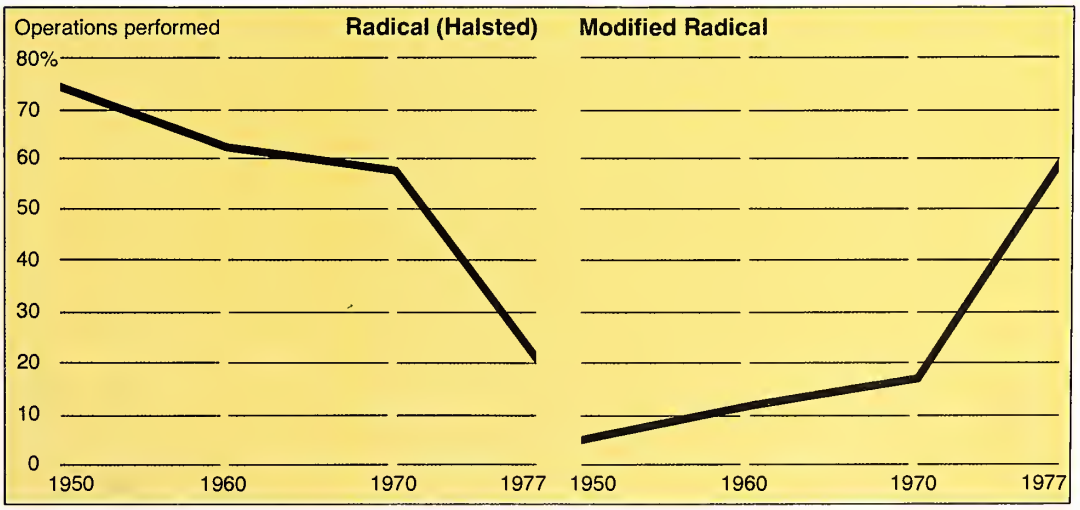
Halsted's approach was based on the belief that cancer cells spread from the tumor directly to adjacent tissue. He thought the major travel route for cancer cells was the lymphatic system and that the bloodstream had no significant role in transport. Further, he assumed that the lymph nodes, small masses of tissue located along the lymphatic vessels, were highly effective in trapping tumor cells and keeping them from escaping into the body.

Halsted devised his technique for women with widespread breast cancer. Though mutilating, it bought for women with previously incurable disease a chance for survival. Soon, women began going to physicians earlier, with smaller, generally more highly curable, cancers. They too were treated with radical surgery. And while survival rates continued to rise during the early part of this century, they began to level off around 1950. Even improved technology, with blood transfusions, better antibiotics, new anesthetics and refined surgical techniques, has had no major impact on survival.

Outlook has improved for breast cancer patients like Barbara Chambers, facing page. In 1894 surgeon William Halsted, below, devised operation that removed entire breast, lymph nodes and chest muscles, based on belief that cancer spreads to adjacent tissues. In 1960s Bernard Fisher, left, headed studies revealing cancer cells spread through bloodstream, identified systemic nature of the disease. Graph shows trend away from traditional Halsted radical mastectomy toward operation that preserves chest muscles.

In the mid-1960s, studies by Dr. Bernard Fisher and his colleagues at the University of Pittsburgh gave rise to a hypothesis that differed from established beliefs about the spread of cancer cells. Fisher reports, "This work revealed that whether tumor cells initially travel via the bloodstream or via lymphatics, the two vascular systems are so interrelated that it is impractical to consider them as independent routes for spread of cancer. There appears to be no orderly pattern to the way cells spread."

When researchers discovered cancer cells in the bloodstreams



of persons with disease, they also observed increased numbers of these cells after any manipulation of the tumor site, even as slight an action as washing the skin over the tumor before undertaking surgery. At one time, they had thought that cancer cells were dislodged into the circulation by the trauma of the surgical procedure. Early on, they conceived the idea that giving systemic, or body-wide, therapy immediately after surgery might destroy these circulating cells.

"We now recognize that cancers shed cells from the beginning of their growth," says Fisher, "and everyone with cancer has some cancer cells circulating in the bloodstream. Lymph nodes may be a way-station for some cancer cells, but they do not serve as an effective barrier. In sum, breast cancer appears to be a systemic disease from its very start."

The surgeons of the National Surgical Adjuvant Breast Project began in 1958 a modest clinical study. They gave one group of women an anticancer drug during the 2 days immediately following a radical mastectomy. A second group of women did not receive drugs. Five years, even 10 years later, the treated women were doing significantly better.

Nearly a dozen other drug studies were begun between 1958 and 1972. While most purported to show beneficial results with drug therapy, the number of patients involved was small and the evidence was not clear-cut.

In the early 1970s, the National Surgical Adjuvant Breast Project, a National Cancer Institute-funded consortium of more than 100 medical centers nationwide, began two studies. One evaluated a less extensive surgical procedure for treating breast cancer; the other the value of anticancer drugs given right after surgery in prolonging survival.

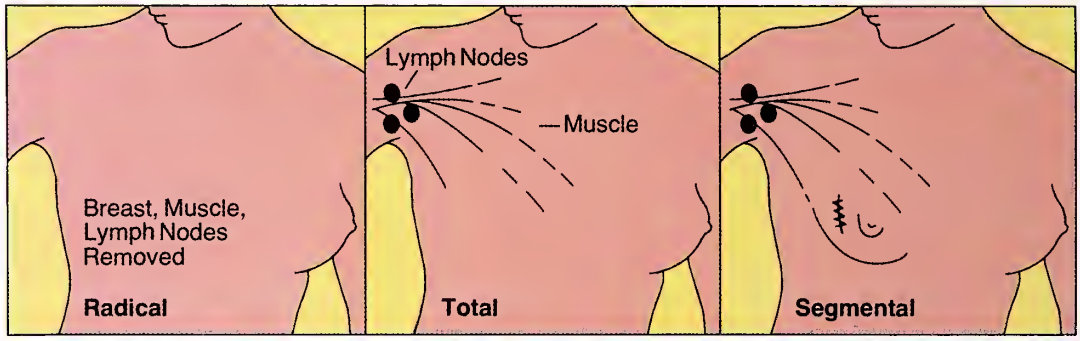
The women who participated in the surgical trial had small breast cancers with no obvious spread of the disease to the lymph nodes in the underarm area. A computer chose which of the following operations a woman would receive:

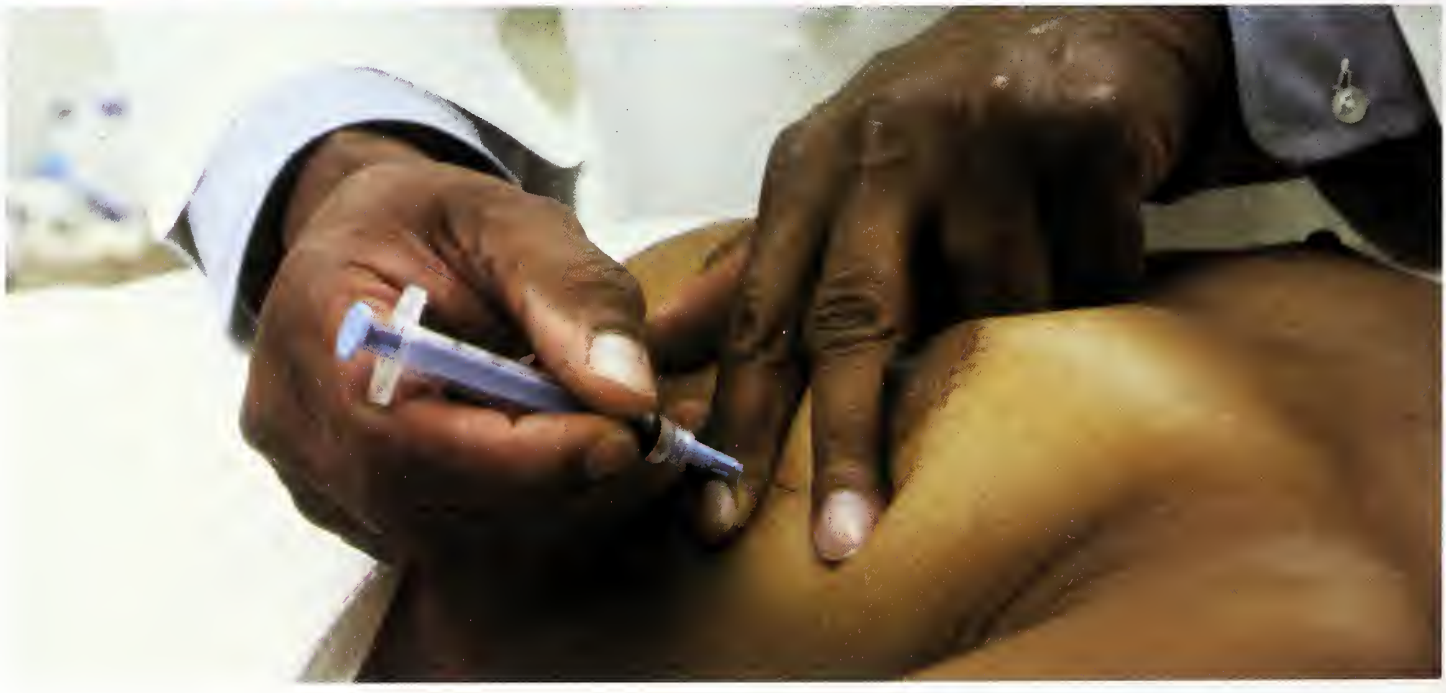
☐ Radical mastectomy

☐ Total mastectomy (involving complete removal of the breast but not the lymph nodes or chest muscles) coupled with x-ray treatment of the breast and adjacent area.

☐ Total mastectomy followed

Monthly breast self-examination is aid to discovering cancer when it is small and most treatable. Eighty-five percent of American women are now diagnosed at an early stage. Most lumps are not cancer. Needle biopsy, below, tells whether breast lump is fluid-filled cyst or solid tumor; if cyst, drainage provides effective treatment. If solid, surgical biopsy, right, yields definitive diagnosis. Surgeon and pathologist, bottom right, view biopsy tissue for presence of cancer cells. Diagram, below, shows three types of breast surgery. Halsted radical mastectomy removes breast, chest muscles and lymph nodes in underarm area. New standard treatment removes breast and a sample of underarm lymph nodes. Segmental mastectomy or lumpectomy, now being evaluated, removes tumor and wedge of breast. Patient shown far right bottom had segmental surgery of left breast. Small scar near armpit shows where tumor and some normal breast tissue were removed. Chest muscles are preserved in new standard operation, far right above.

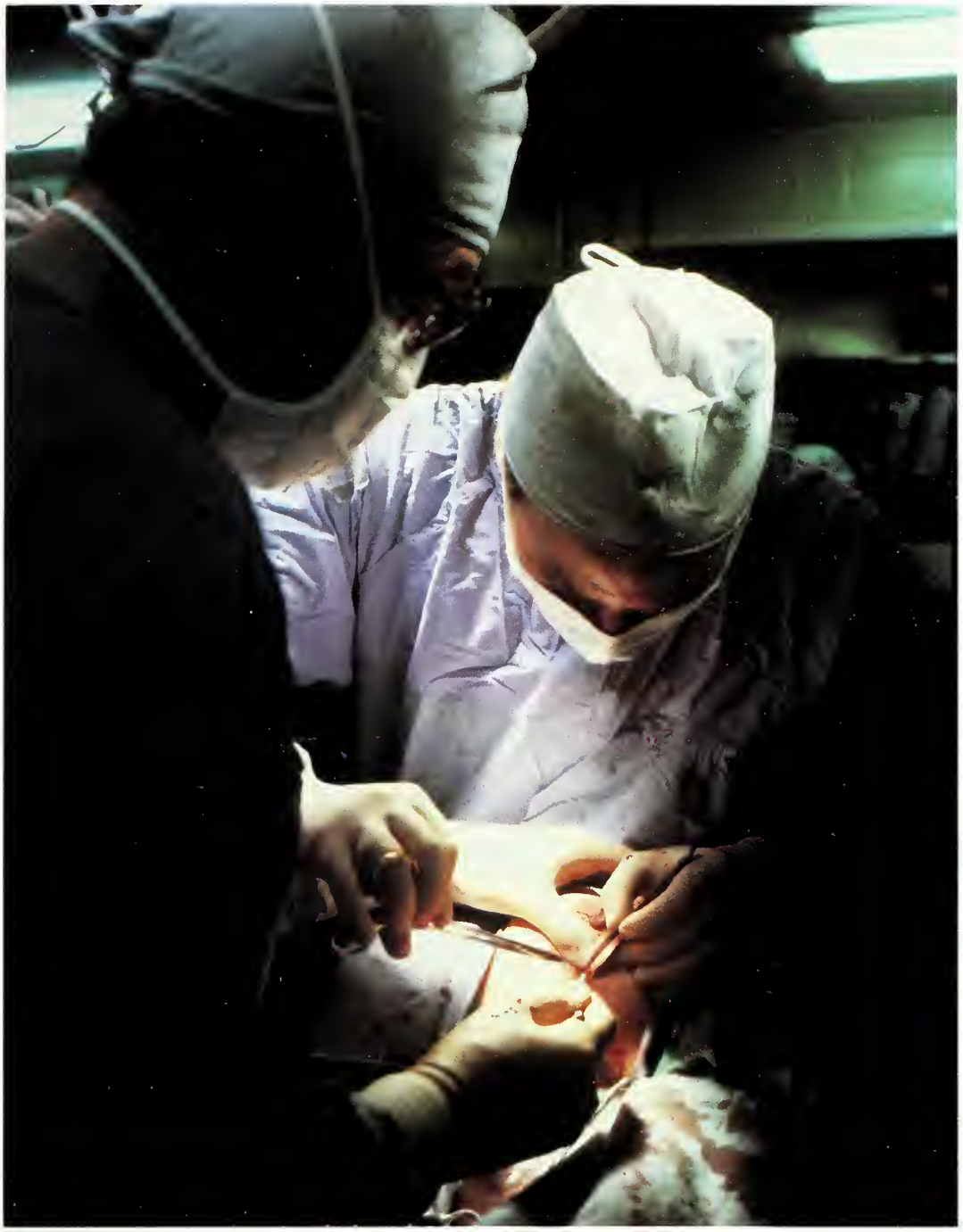


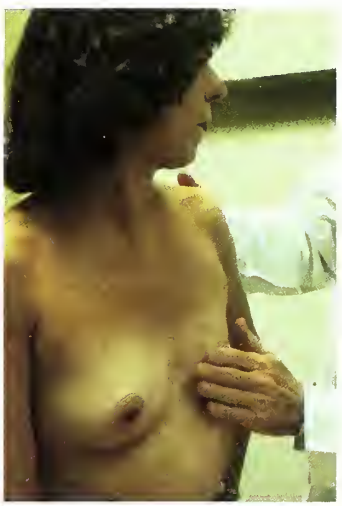


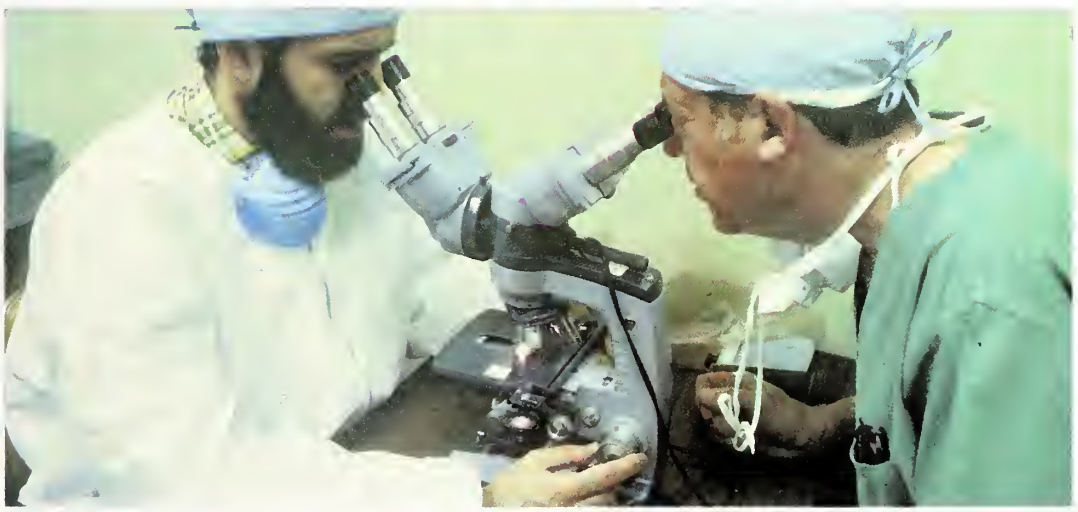
later by removal of any lymph nodes that show cancerous changes.

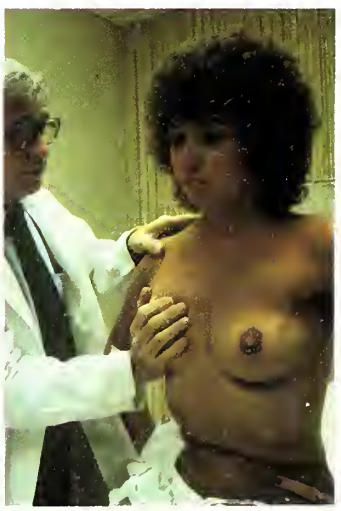
The study involved more than 1700 women. Among the three treatment groups, no significant differences were found in recurrence of disease in the breast or elsewhere, or in patients' survival. These results led to a major revision in surgical practice for breast cancer.

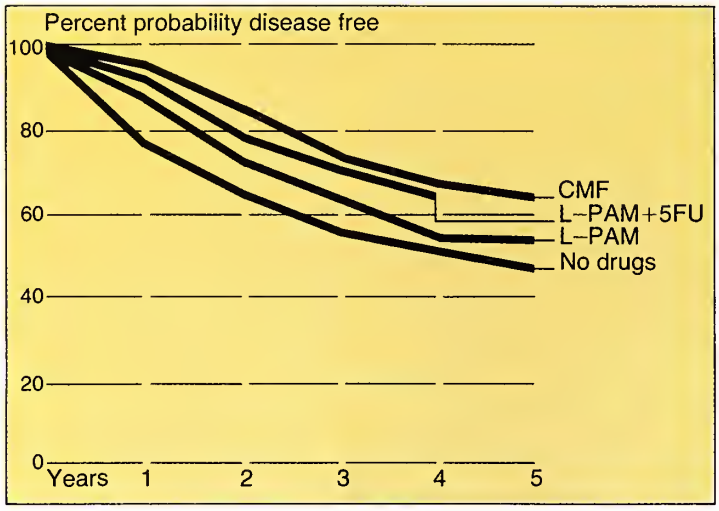
At an NIH Consensus Development Conference in 1979, experts in breast cancer surgery agreed that for women with localized disease, Halsted radical mastectomy—the traditional treatment for the past 80 years—should be set aside in favor of a procedure that preserves the chest muscles. The panel concluded that total mastectomy with axillary dissection of lymph nodes should be recognized as adequate treatment for small breast cancers. Fully 85 percent of American women who get breast cancer discover it early enough to qualify











for this less extensive surgery.

Axillary dissection involves making an incision in the armpit and removing a variable number of lymph nodes. The procedure is not correctly described as a "modified radical" or a "total mastectomy." "Total mastectomy with axillary dissection" is the new preferred terminology. In this procedure the nodes are removed and examined for the presence of cancer, a procedure of great importance in making decisions about further treatment.

Studies are under way to determine whether a breast-conserving operation known as a partial or segmental mastectomy, also with axillary dissection, is as effective as total mastectomy with axillary dissection. In this procedure, only that portion of the breast containing the cancer is removed, along with a surrounding margin of breast tissue.

The number of nodes in the axilla, or underarm area, that contain cancer cells is viewed as an important predictor of extent of the disease and therefore, the odds of survival. There is a sharp rise in recurrence rate when four or more nodes are involved.

In 1972, the National Surgical Adjuvant Breast Project launched a plan to evaluate a number of drugs in sequential fashion for breast cancer patients with positive nodes. This plan was based on the success of their earlier

A Test for Choosing Effective Therapy

The estrogen receptor assay provides an important guide for selecting appropriate treatment for the breast cancer patient. It is performed on a sample of tissue taken from a breast tumor at the time of surgery. By indicating whether the tumor is the kind that binds and retains the female hormone estrogen, the test predicts whether hormone manipulation, such as removal of ovaries or adrenals, or the use of antiestrogenic drugs, will be effective.

If the tissue sample contains adequate quantities of receptors, which are steroid-binding proteins, it is likely the cancer will respond to estrogen deprivation. But if there are few or no receptors in the tumor, surgical removal of the ovaries or adrenal glands would be needless and could reduce the patient's tolerance for alternative treatment, such as chemotherapy. Thus the test is of great importance when crucial decisions must be made.

Elwood V. Jensen, a Chicago cancer researcher, discovered the receptor substance in animal studies he started in 1958. He was trying

Estrogen receptor assay, developed by Elwood Jensen, right, is done at time of mastectomy. Results suggest whether removal of ovaries or use of antiestrogen drugs are likely to be effective. Photos show steps involved in the analysis.

Use of two or more drugs right after surgery has delayed recurrences for women with breast cancer that has spread to the lymph nodes. More than 4,000 women have participated in these studies. Chart, center left, shows percent of women who remain free of disease following surgery alone; surgery accompanied by treatment with one drug, L-PAM; surgery and two drugs, L-PAM plus 5FU; and surgery and three drugs, CMF. Drugs reach cancer cells in all parts of the body. Vincent T. DeVita, left, directs the National Cancer Program that supported studies in both the United States and Italy. Investigators have used various combinations of some 15 different drugs, far left.

study showing prolonged survival in some women given drugs right after surgery. Although combinations of drugs were coming into vogue as a result of their success in other cancers, such as childhood leukemia and Hodgkin's disease, the project's investigators felt that starting with a single drug would establish a valuable point of reference.

The group began by comparing one drug with placebo, that is, a nonactive substance. They then compared the one drug against two, then the two drugs against three, in various combinations. Five different studies have been undertaken to date; more than 4,000 women have enrolled. The specific drugs tested are:

- ☐ L-PAM
- ☐ L-PAM plus 5 fluorouracil (5-FU)
- ☐ L-PAM plus 5-FU plus methotrexate
- ☐ L-PAM plus 5-FU plus tamoxifen
- ☐ L-PAM plus 5-FU plus *C. parvum*

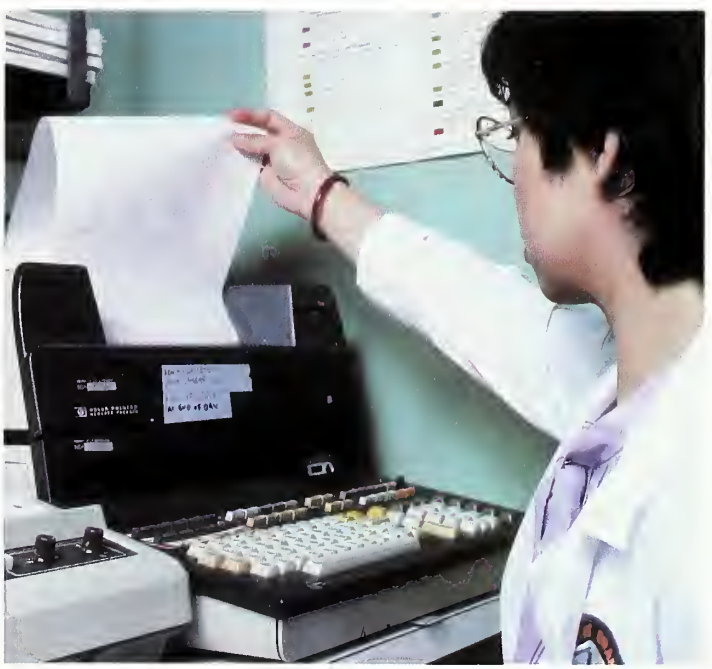
Since 1973 the National Cancer Institute has funded an investigation at the National Cancer Institute of Milan, Italy, under the direction of Dr. Gianni Bonadonna. These researchers also are examining combinations of drugs postsurgically for women with positive nodes. In their first study, they gave their patients Cytoxan, methotrexate and 5-fluorouracil (CMF). Nine hundred

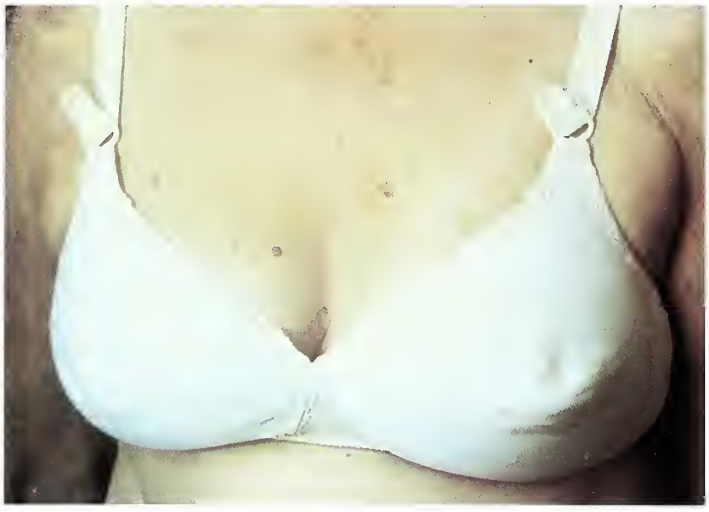
to find out how estrogen causes female reproductive tissues to grow. His work on human tissue began in 1966, when he was able to demonstrate that patients whose breast cancer lacked the hormone-binding substance had little chance of responding to hormone treatment. Receptor-rich cancers—those with plentiful quantities of receptors—appear to represent a different form of the disease that grows more slowly. About one third of women tested have estrogen receptor-rich cancers.

Originally, the estrogen receptor assay's major purpose was to predict the chances for successful hormone treatment if and when the cancer recurred. Today it is increasingly being used in early disease to guide drug treatment given in addition to surgical removal of tumor and lymph nodes.

At a 1979 NIH Consensus Development Conference, a panel including research scientists, practicing doctors, patients, and others with special knowledge or strong interests in the test, confirmed the usefulness of the estrogen receptor assay and called for more widespread application of it. Panel members reaffirmed findings that few patients with cancers negative for receptors would respond favorably to removal of estrogen-producing glands such as adrenals or ovaries or to antiestrogenic drugs such as tamoxifen, but more than half of patients with receptor-rich tumors can be helped by these procedures. There is no proven connection between estrogen receptor status and the potential success or failure of cancer chemotherapy.

The test is done now mostly in special laboratories, and requires freezing of samples immediately after surgery to protect the delicate receptor proteins during transport. To make the testing more widely available, quicker, and less expensive, work is advancing on new test methods that can be done by technicians in local hospitals, eliminating the need to ship samples to specialized laboratories. Such tests could take practical steps toward fulfilling the recommendation of the consensus panel calling for estrogen receptor assays of every breast cancer at the time of surgery. Results of the assay would be useful not only to guide the course of initial therapy but also in the event the disease recurs, even several years later.





With trend toward simpler surgery, as many as 80 percent of women who undergo mastectomy may be eligible for breast reconstruction, far right. Surgeons implant a flexible sac filled with silicon gel into the chest just under skin, right. Size is subtly adjusted by inflation with air or injection of saline. Operation enables women to look good in their clothes and to have a better self-image, left. Some women later choose to undergo a second operation to reconstruct a nipple, made from grafting skin from opposite nipple or groin fold of inner thigh. Improvements of 1970s, both in implant materials and in technique, allow surgeons to reconstruct more natural looking breast.

women participated in the trial.

Early findings from these two major research efforts were made public in 1975. The significant rise in both disease-free interval and overall survival continues for women treated with two or more drugs following surgery. In additional studies in the United States and elsewhere, independent investigators have used various combinations of some 15 different drugs.

Dr. Vincent DeVita, Director of the National Cancer Institute, testified before Congress: "These clinical trials in breast cancer are extraordinarily important because they have demonstrated that the use of chemotherapy after surgery is feasible, and more important, that such therapy works."

Drug treatment has some worrisome drawbacks. Its side effects reflect the action of drugs on rapidly dividing normal cells in the body, in areas such as the bone marrow, where blood is formed; the lining of the gastrointestinal tract; the hair follicles, and the skin.

Most side effects are acute and limited to the time treatment is being taken, but the possibility exists that serious problems may occur 10, even 20 years after treatment.

The most common acute side effects are nausea and vomiting, diarrhea, mouth ulcers, hair loss, loss of appetite and general mal-

Pioneer for Patient Options

Rose Kushner is a feisty lady.

When she discovered an apple-seed sized bulge in her breast in 1974, she called 18 surgeons before she got one to agree to perform only a biopsy. At that time many physicians believed that if cancer were present the exploratory surgery would trigger the release of cancer cells into the body, and that the best offense was an immediate mastectomy.

But Rose wanted time to consider her options.

She also wanted time to adjust to the idea of losing her breast.

When the lump proved to be malignant, she sought the advice of breast cancer specialists before deciding to have a modified radical mastectomy, a procedure in which the chest muscles are left intact.

Her difficulties in arranging for the two-stage treatment and in finding information to help her with her decision prompted her to write an article about her experiences for The Washington Post. The article appeared in print just after former First Lady Betty Ford had her well-publicized mastectomy.

Continued page 24

Rose Kushner, who herself has had breast cancer, campaigns for women to understand options available to them before they undergo mastectomy. She answers questions from women with breast cancer, provides data to help them in decisionmaking. Daughter Lesley often helps.

aise. About 80 percent of all women experience some of these side effects, some minimally, some severely. Drugs used to treat more extensive disease are most likely to have side effects.

The problem many women find particularly devastating is hair loss. For women with advanced disease taking adriamycin, a drug that ordinarily induces hair loss 98 percent of the time, scientists have found that chilling the scalp before and after the drug is given can reduce to 40 percent the number of women losing their hair. Physicians believe that the cold may decrease the amount of drug that penetrates the scalp.

Potential long-term effects from drugs include sterility, heart damage and second cancers, most notably leukemia. Patients on chemotherapy must be closely watched. In addition to physical checkups every 3 or 6 months, they usually have periodic blood tests, chest x-rays, bone scans and mammograms.

Some women find the continuing treatment, and the physical discomfort that frequently results, a constant and painful reminder that they have a potentially fatal disease. Others more optimistically view chemotherapy as "mopping up" after surgery to finish off remaining cancer cells.

Only a few studies of the emotional aspects of post-mastectomy treatment have been conducted. In one study of 50 women who had completed 1 year of the 2 year drug treatment, investigators found that some degree of life change and emotional distress was very common, if not universal. The researchers examined sexual and family relationships, financial situations and levels of general and work-related activity. Previous studies indicate that by the end of the first year follow-

The Experience of Survival

Barbara Chambers was 36 when she discovered a lump in her breast.

Following her mastectomy, Barbara's surgeon called her husband at midnight with the pathologist's report: 16 of the 27 lymph nodes removed contained cancer cells. Barbara might have only 6 months to live.

"My surgeon encouraged me to see an oncologist. I had never heard about drug therapy before.

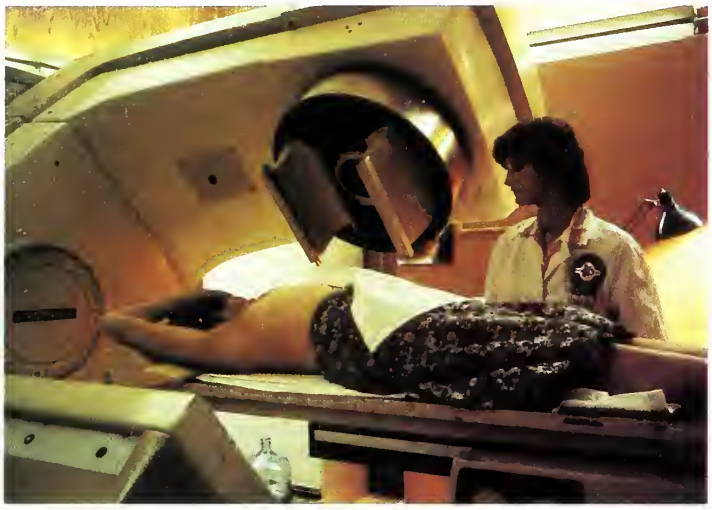
"Since I live in Washington, D.C., a doctor friend referred me to the National Cancer Institute. There I learned that only one woman in ten with my type and stage of cancer lived for 5 years after surgery without a relapse, and that recurrences of my type of cancer usually came within 18 months. I learned about all the types of drug therapies, where they were being given and what the possible long-term effects were.

"I agreed to go on a combination of drugs that included adriamycin.

"My year-long treatment was given in 28-day cycles, with injections

Continued page 25

Barbara Chambers was diagnosed with breast cancer at age 36. Surgeon said she might live only 6 months. Barbara participated in clinical study, received anticancer drugs following surgery. At the three year mark, she is well and free of disease.



In mid 1970s many centers in United States began evaluating use of radiation therapy as primary treatment for women with breast cancer, based on success of procedure in several European centers. This procedure, which leaves a woman with a nearly normal breast, is still experimental. First step is surgical removal of tumor. Then supervoltage linear accelerator, left, delivers x-rays to cancer cells in breast, surrounding lymph nodes and underlying chest wall muscles. Treatment takes about 5 weeks. Patient then receives boost or extra dose of radiation to tumor area by implanting radioactive iridium seeds. Photograph at near right shows surgical placement of tubes. Seeds are later inserted in tube, far right, and remain for 2 days. Patients report procedure is relatively painless.

ing mastectomy, only 12 percent of women receiving drug treatment reported a complete return to their previous level of activity. But by the end of 18 months, the vast majority had resumed normal activity.

Health professionals providing chemotherapy feel that drugs with less toxic effects will cause fewer emotional problems. Some also suggest that a woman who elects not to take recommended therapy may suffer guilt later at not having done everything she might have.

In July 1980, an NIH Consensus Development Conference affirmed the value of drug treatment for premenopausal patients with laboratory evidence of involved nodes. The consensus panel concluded that use of an established combination of drugs appears indicated and that these drugs should be given at full dosage, since lesser amounts have shown inferior results.

In regard to postmenopausal women, the panel noted that ongoing studies seem to show early benefit from adjuvant drugs but said it still is too early to make a recommendation.

For women with no evidence of cancer cells in the lymph nodes, the panel felt that the use of adjuvant chemotherapy may expose

Soon the phone was ringing at Rose's suburban Washington home. Women were hoping she could answer their questions about breast cancer. "That was the unofficial beginning of the Breast Cancer Advisory Center," she relates. A prize-winning medical writer, Rose expanded her article into a book, now published in paperback as *Why Me? What Every Woman Should Know About Breast Cancer to Save Her Life.*

Proceeds from the book helped fund the telephone hot-line, staffed by a registered nurse. Rose's television appearances and newspaper interviews triggered as many as 100 calls a day. Though royalty funds have petered out and she no longer can afford the nurse's salary, she continues to keep the service going.

"I don't give advice, I give data," she explains. "When women ask for referrals, I give them names of two physicians from opposing schools and tell them about ongoing clinical trials." She also answers mail addressed to the Breast Cancer Advisory Center, and she refers some callers to the nationwide toll-free Cancer Information Service run by the National Cancer Institute.

"One area that's especially troubling is the lack of pre-surgical counseling. Some women never tell their husbands about the lump until after they go for a biopsy. For every woman whose lump turns out to be cancer, there are six others whose lump is benign. Yet many women put off going to the doctor because they're afraid to face the possibility of cancer."

She asserts: "Supportive counseling should be an institutionalized part of medical care, from the time a woman first walks in the door for a biopsy."

She has written a booklet, *If You've Thought About Breast Cancer*, that answers some of the questions she most frequently is asked. It discusses choice of physician, the type of exam to expect, biopsies, mammograms, surgical procedures, radiation treatment, adjuvant chemotherapy and breast reconstruction. The booklet is distributed by the National Cancer Institute.

As the only nonphysician member of the NIH Consensus Development Panel on The Treatment of Primary Breast Cancer, Rose was instrumental in moving the panel to endorse a time lapse between the diagnostic biopsy and further surgery.

She cites with pleasure the passage of a 1980 Massachusetts law specifying that breast cancer patients have the right to "complete information on all alternative treatments which are medically viable."

Rose recently was named to the President's National Cancer Advisory Board. She is one of six lay persons on the 18-member panel charged with overseeing policy for the National Cancer Institute.

Rose is adamant about a woman's assuming responsibility for her own well-being. She insists: "Every woman should be aware of all options open to her and should participate when decisions are made."

the majority to risks of toxicity without benefit. Researchers are trying to identify those women with negative nodes who are most likely to have a recurrence and for whom drug therapy might be beneficial.

"It has become apparent that no one drug works best for all women or for all forms of breast cancer. We are coming closer to our goal of being able to recommend specific treatments," reports Dr. Fisher. "But we can't yet provide sure fire recipes."

Dr. Fisher sums up: "For the woman with a lump in her breast, treatment that was the standard only 20 years ago today is an anachronism. The woman no longer is treated as an emergency. She is apt to have an outpatient biopsy; will have a thorough evaluation for metastases; may have a second opinion; will not have a radical mastectomy; will engage in a clinical trial to evaluate breast-conserving operation; will have postoperative chemotherapy within a clinical trial if she has positive nodes; will be part of a meticulous followup program; will receive psychosocial rehabilitation if necessary; and above all, is likely to live longer, well."

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and blood counts on day 1 and 8 and additional blood counts on day 15. The days I got the injections I vomited for 12 to 18 hours straight. I had severe migraine headaches. Within a month after beginning treatment, I was bald. I had mouth sores and my sense of smell was heightened. Eventually I vomited walking in the door of the NCI for treatment. My white blood cell count dropped dangerously low and I had to be hospitalized for 10 days.

"Nonetheless, I would do it over again.

"My husband made it absolutely clear that the issue was my life. Up until then I had framed my life around his. Now he handled car pools and piano lessons; he didn't take any business trips for 6 months. He works as a lawyer and arranged his schedule so that he could take off work the day I received treatment and the next day as well, in order to be with me. There I was, minus a breast and bald as a berry, but we became even closer."

Friends flocked to her side. "No dinner was cooked in this house for at least 2 months," she recalls.

With their daughter and son, then 10 and 7, Barbara shared the facts of her illness as she learned them, at a level she felt the children could understand. On treatment days her daughter often spent the night with a friend. Her son preferred to stay home. Her daughter picked "cancer" as the topic for a school science report.

For the first few months every holiday was traumatic. Barbara worried that she might not be alive for another one. She burst into tears at Thanksgiving dinner.

Hereditary aspects of breast cancer are a continuing source of anxiety. Barbara comments, "The possibility that my daughter some day might have to undergo mutilating surgery enrages me."

During the year she received chemotherapy, Barbara continued her work as director of the Columbia Road Children's Center, a school and day-care facility. But her customary 50-hour week had to be adjusted. Her view about how her job should be done, and concern about how she would manage if she had a relapse prompted her decision to change. She returned to college for her master's degree in social work. In June 1980, with another social worker and a psychiatrist, she set up a counseling center for persons with cancer and other chronic diseases.

It's been 3 years since her mastectomy. She has not had a recurrence of her disease. Her hair started growing in about 3 months before the drug treatment was concluded. She looks and feels well.

Through her association with the National Cancer Institute as a patient, Barbara sat as the consumer representative on the Consensus Development Panel on Adjuvant Chemotherapy of Breast Cancer that met at the National Institutes of Health in July 1980.

"Cancer is the ultimate consumer issue," she observes. "Your life is on the line. The side effects of drug treatment can't be minimized. But I knew what my odds were. I'm aiming for a home run."


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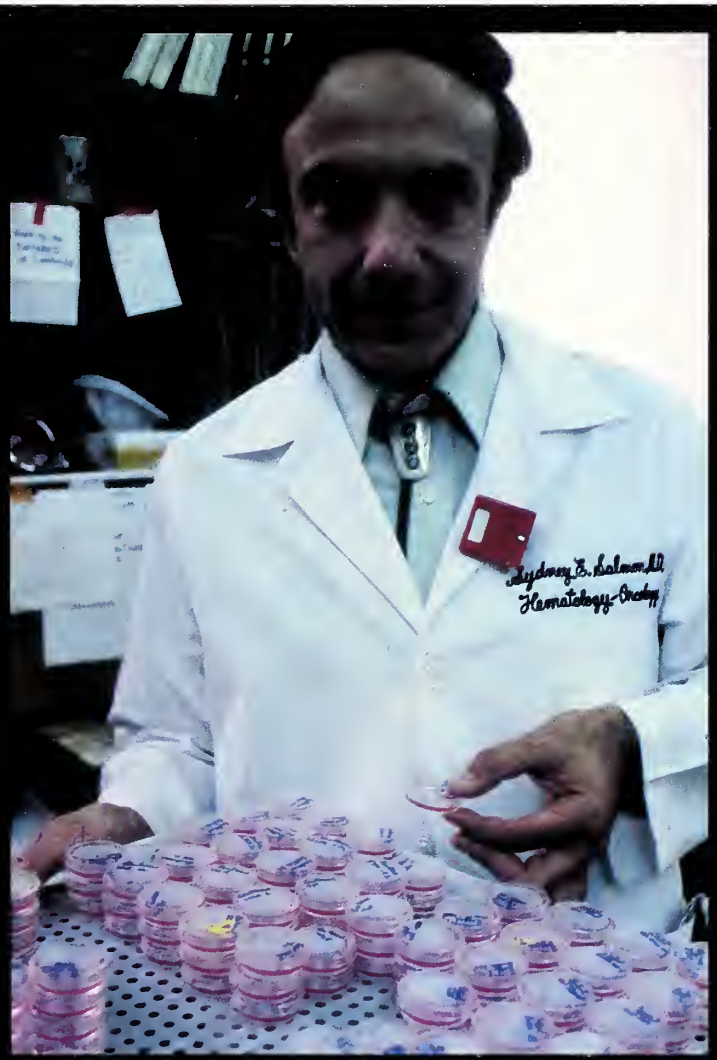
The National Cancer Institute plays an important role in the development of anticancer drugs. Several introduced in the 1970s have made an impact on treatment of cancer. Cisplatinum, for example, has doubled the rate of complete responses for patients with testicular cancer. Other drugs synthesized by chemists include the nitrosoureas. These drugs are unique—they cross the blood-brain barrier to attack cancer cells hidden in the brain. Under sterile conditions, technicians process antibiotics active against cancer, middle right. Mixer, lower right, contains fermentation broth of soil microorganisms that make Adriamycin. Early studies of biologics, such as interferon, are promising, but large amounts of drug, which is made by human cells growing in roller bottles, above right, are needed. Dr. Sydney Salmon, below, and colleagues at the University of Arizona found a way to grow human cancer cells in laboratory dishes, thus providing an easier way of testing a drug's activity against various forms of human cancer.



During the 1970s, research into causes and risk factors associated with cancer focused strongly on the environment and on variations in people's lifestyles. The air we breathe, the foods we eat, the water we use, the work we do, and whether or not we smoke all have a potential bearing on our chances of getting cancer.

The presence of chemicals in the human environment is a fact of contemporary life. Though substances capable of causing cancer are believed to be only a small percentage of the entire number of chemicals, it is essential to identify them. Biological testing for carcinogenicity, or ability to cause cancer, is important for cancer prevention. Once a carcinogen is identified, precautions can be taken to eliminate it from the environment or to limit people's exposure.

Data gathered by epidemiologists identify populations in which various types of cancer occur more frequently. Such information gives these medical detectives clues about factors that increase a person's risk for developing cancer. These scientists also have identified populations with lower than average risks for cancer, leading to potentially useful lessons on living habits and geographic locations.

In the last decade, we saw much new knowledge collected and a measure of progress made in controlling exposure to carcinogens. In the next decade we can and must do much more.

II.

Lifestyle, Environment and Cancer

Lifestyle, Environment and Cancer

PEOPLE WATCHING AND FACTS OF LIFESTYLE

Much of what we already know about cancer has come not from the laboratory, but from studies of people and how they live.

The studies that established a link between cigarette smoking and lung cancer, for example, grew out of observations by a number of investigators who noticed that those who smoked cigarettes seemed most susceptible to lung cancer. In the early 1950s Sir Richard Doll, a London physician, performed large-scale studies that confirmed these initial suspicions.

The first known case of occupational cancer was discovered from similar observations by another London physician, Percivall Pott, in 1775. He observed that the rare cancer of the scrotum was seen almost exclusively in chimney sweeps. These poor lads were human brushes hauled up and down the soot-choked chimneys of London. Pott reasoned that some element of soot was responsible, and more than 100 years later, benzo(a)-pyrene, a combustion product, was found to be a powerful animal carcinogen.

Studies like these show us how certain cancers occur and also show us how we can prevent such cancers.

The study of populations and disease is termed epidemiology (from the Greek words **epi-**, among, and **demos**, people). Epidemiologists are the Sam Spades of medicine. Their work is the painstaking accumulation of clues and bits of evidence to help them solve the mystery of various disease occurrences.

Epidemiologist Brian MacMahon of the Harvard School of Public Health describes the field as "the study of the distribution and determinants of disease frequency in man." Another epidemiologist, Brian Henderson of the University of Southern California, says, "The human population is our laboratory."

Traditionally, the epidemiologists have been chiefly concerned with epidemics—acute outbreaks of infectious disease. It was they who suggested causes of the outbreaks of cholera or of meningitis. They can take some of the credit, too, for ridding the world of the major scourge, smallpox.

Now, though, epidemiology is no more restricted to the study of outbreaks of disease than meteorology is to the study of hurricanes. Epidemiologists have taken on a new task: cancer—the industrial world's number two killer.

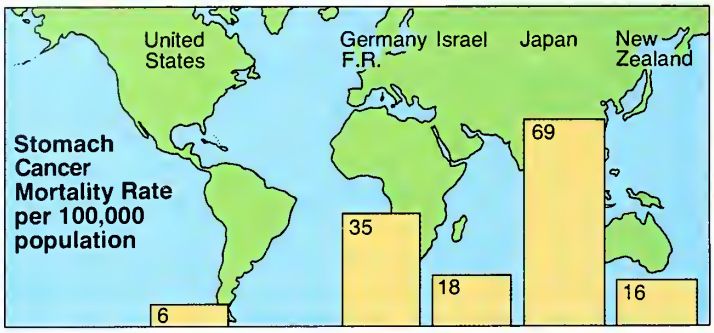
In the past decade, cancer epidemiologists have turned to our environment and our lifestyle in their search for clues. Where once scientists saw that one or two kinds of cancer might result from aspects of lifestyle or environment, there's now a growing suspicion among epidemiologists that most of the diseases called cancer may be related to the way we live—what we eat, whether we smoke, where we work, whether we live in the city or the country, if we're married or single, when we choose to have our children, what we do in our spare time.

Population studies tell us much about how cancer is caused and how we can prevent it. Link between cigarette smoking and lung cancer, for example, was established by Sir Richard Doll, below. One of earliest cases of occupational cancer, seen in chimney sweeps, was observed in the 1770s by Percivall Pott, center. Brian Henderson, left, of Los Angeles is one of new breed of cancer epidemiologists looking at other links between lifestyle and cancer. He was among researchers who spotted cancer-causing effects of postmenopausal estrogens.

John Higginson of Geneva, Switzerland, is the founding director of the World Health Organization's International Agency for Research on Cancer. He and others noted that the occurrences of different types of cancer differ widely among the inhabitants of different countries. By regarding the low incidence of a cancer in one country as a baseline, they showed that death rates for specific cancers varied by as much as 100-fold in different locations throughout the world. They reasoned that environmental and cultural differences might account for these wide differences.

We're learning, too, that the environment is more than a static landscape. Our understanding of the environment must take into account how we live with it.

Biostatistician Marvin Schneiderman, formerly the NCI's associate director for science policy, observes: "If we were Australians we would go out in the sun wearing relatively little clothing, and partly because our ancestors were all fair-skinned, we'd have red foreheads and red noses and the highest skin cancer rates in the world. If we were Bedouins (or Noel Coward) we would know that was insane behavior and we'd go out in the sun only when covered



completely from head to foot."

Thus, our environment may be asphalt or rain forest or desert, but our lifestyle tells us what to wear in it and when. Who our ancestors were plays an important role in our chances of getting cancer—but the shoes of custom and habit we put on each morning may prove to be the most important of all.

Other studies that focused our attention on lifestyle were those of migrants. One such study, done in the late 1960s, looked at Japanese who migrated to this country. In Japan, cancer of the stomach, for example, is five times more common than it is here, but cancer of the large intestine, breast, and prostate are far less common. The study showed that when the Japanese moved to this country these differences begin to disappear over successive generations. Thus, cancer of the stomach decreases among Japanese-Americans in this country, while cancers of the large intestine, breast, and prostate all increase significantly in them.

The genetic make-up of people who develop cancer is an important factor, but these and other migrant studies indicate that people tend to do things differently when they move to a new country, and what they do has a bearing on their chances of developing cancer after they get there.

Rare cancers that occur in unusual circumstances are often spotted by alert clinicians. That was the case with chimney sweeps. It was also the case with the rare, clear cell adenocarcinoma of the vagina first seen in young girls in 1966. These cases

Cancer Is Sometimes a Family Affair

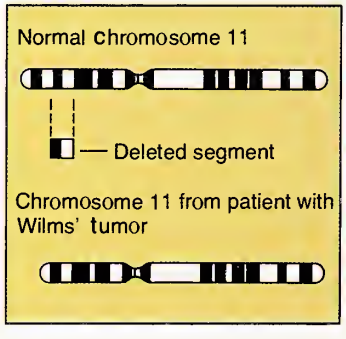
Is cancer caused by something in the environment, or is it due to our genes?

The answer is most probably a combination of the two. Geneticist John J. Mulvihill, of the NCI's Clinical Epidemiology Branch, says it's "a matter of common sense" that people differ in their response to carcinogens.

Not all heavy smokers, for example, develop lung cancer, and not all people who get lung cancer are heavy smokers. So it appears from this example, and a growing number of others, that some people at high risk of cancer are those born with a predisposition—whether inherited or acquired—who are then exposed to one or more carcinogens.

Medical geneticist Alfred G. Knudson, director of the Institute for Cancer Research in Philadelphia, describes the phenomenon as the "hypothesis of multiple events." According to this theory, at least two independent events have to occur to change a normal to a cancer cell. "The presence of a mutant gene is one event but is not by itself enough. But those with hereditary predispositions require one less event than

Clinical epidemiologists Robert W. Miller and John Mulvihill of NCI are looking at genetic aspects of cancer. Pictured, far right, the eyes of an identical twin. Both twins lack irises. Both have missing chromosome segment, right, associated with Wilms' tumor.



Cancer incidence rates may vary sharply from country to country as seen in chart for stomach cancer far left. Differing habits, diet and environment are suspected culprits. Studies of migrant groups strengthen suspicion. Japanese, for example, who emigrate to California, change their pattern of cancer incidence within a generation or two: They develop less stomach cancer and more colon cancer. Because Japanese-Americans tend to marry among themselves—thus ruling out genetic factors—other lifestyle factors, such as diet, are suspected causes as these migrants adopt Western customs.

were later linked with diethylstilbestrol (DES) used by their mothers during pregnancy. Five years of comprehensive studies showed the cancer risk to be less than initially feared. But DES daughters, some of them still very young, may still have some problems with their own pregnancies.

Country-by-country dissimilarities in cancer incidence can be spotted relatively easily, too. But how can our medical detectives pick out clues about cancers that are common, not rare? How can they spot disproportionate numbers of cancers within a country? And how can they point a finger at aspects of the environment and lifestyle that may contribute to the development of cancer 15 or 20 years later?

Two major accomplishments in the past decade have helped epidemiologists everywhere in their search for these clues. One of these was the publication by the National Cancer Institute of computer-printed maps that show, county by county, the death rates for specific cancers. The other was formation of a network of hospitals and tumor registries that continuously collects data on incidence and survival of cancer cases. It is known as the SEER program (Surveillance, Epidemiology, and End Results).

Most industrialized nations today have systems for keeping "vital" records (births, deaths, marriages, and divorces). In the United States, state laws require that these events be registered as they occur. Local registrars send these records, in turn, to state registrars who keep permanent files and send copies to the National Center for Health Statistics (NCHS) for tabulation of national statistics.

Beginning in 1902, under the terms of a death registration act, copies of actual death certificates were collected annually by a permanent bureau of the census; and by 1933 this system had grown to include the entire United States. The standard death certificate developed by the NCHS includes demographic data—place of residence, occupation, national origin, age, sex, and specific cause of death.

In 1975, using these data combined with 1970 U.S. Census data, the NCI published the *Atlas of Cancer Mortality for U.S. Counties: 1950-1969*. Four-color maps show geographic variation in cancer death rates for 35 anatomic sites of cancer in most of the counties of the U.S. (In counties with sparse populations, two or more may be combined.) The atlas has separate maps for men and women for each cancer site, a breakdown that helps to distinguish between occupational causes and causes associated with

do nonhereditary cases of cancer, because one event has been inherited."

Many studies over the past decade support this "multiple event" theory for cancer risk. For example, children who develop Wilms' tumor, cancer of the kidney, consistently lack a segment of chromosome. In a study of twins, though, the two were genetically identical—both missing the chromosomal piece—and both showed the malformations that accompany the tumor, among them, a missing iris. Yet only one of the twins developed the cancer.

Comments pediatrician Robert W. Miller, head of the NCI Clinical Epidemiology Branch: "This sort of evidence indicates that there may be a second event—an environmental trigger—that was missing in the twin who did not develop the cancer."

Retinoblastoma, a cancer of the eye, seems to have both genetic and environmental determinants. About 40 percent of retinoblastoma cases are familial and these almost always occur bilaterally or in both eyes. The remaining 60 percent of cases are non-heritable, and occur in one eye only. This form of cancer also raises the issue of "missing events," Miller notes.

Other diseases very clearly predispose a person to cancer. Patients with xeroderma pigmentosum, a skin disease, almost inevitably develop skin cancer when they are exposed to sunlight, because they lack an enzyme needed to repair the damage to DNA caused by sunlight's ultraviolet rays. Thus, notes Mulvihill, patients with this condition "are elaborately oversensitive" to an environmental factor.

Similarly, patients with familial polyposis—the family tendency to develop colon polyps—have an extraordinarily high risk of developing colon cancer; so high, in fact, that surgery is recommended to remove the colon before cancer starts. "This condition would indicate that environmental factors, probably dietary, trigger an event or series of events as the patient grows older," comments Mulvihill.

Recently, a cancer-prone family was identified by scientists at NCI, the Children's Hospital Medical Center in Cincinnati, and the University of Miami working together. They looked into the family background of three brothers who had developed various childhood cancers and found 16 more cancers in six generations. The pattern was similar to that dictated by classical Mendelian laws of inheritance, except that two generations were skipped. This again suggests "missing" environmental events.

Frederick Li of the NCI has studied a family with four generations of renal (kidney) cell cancer associated with a specific chromosome abnormality. The fourth generation has 34 members under age 20, and virtually all who have the chromosome abnormality can be expected to develop the cancer.

Thus, for some forms of cancer, strong interactions exist between genetic predispositions and carcinogenic events in the environment. Miller believes that if each case of cancer were investigated thoroughly in terms of the patient's family history, many more such relationships would be seen. He believes too that as we learn more about predisposing factors, we may be able to protect against additional events.

Miller notes also that the genetic defect, or mutation, that predisposes a person to develop cancer may originally have been caused by an environmental carcinogen. "So perhaps, ultimately, all cases of cancer are environmental," he says.

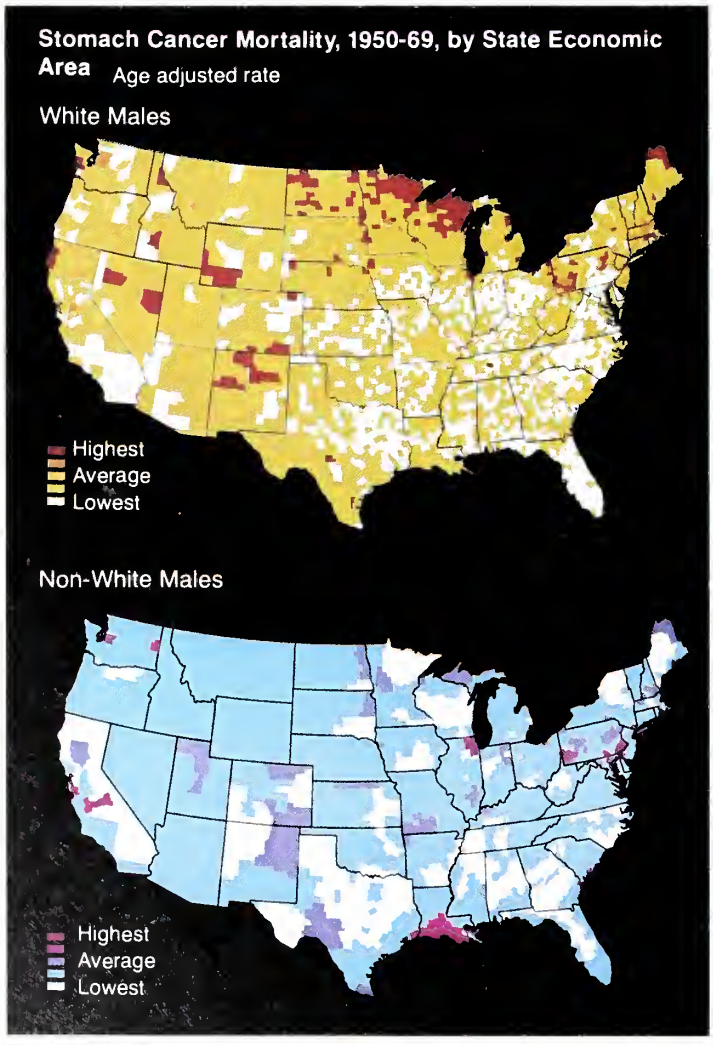
other aspects of lifestyle.

Robert N. Hoover, chief of the Environmental Studies section of the NCI's Environmental Epidemiology Branch, notes that the maps had a powerful impact on the research community and the public.

"The chronic disease epidemiologist—like the epidemiologist who looked at epidemics of infectious disease —is still looking at people who get disease and people who don't and trying to figure out the reasons. We're still looking for unusual concentrations of disease," says Hoover.

"These maps pinpointed the hot spots within the country so we can see where the high rates are. By correlating these hot spots with everything else, we can find out about the people who live there. We now have an entire

Computer printed maps of cancer death rates in all 3,056 U.S. counties were a major breakthrough for epidemiologists. Maps "red flagged" specific demographic and environmental clues to cancer risk. NCI epidemiologists Thomas Mason, Robert Hoover, and Joseph Fraumeni, left, developed these maps. High death rate from mouth and throat cancer among women in the southeastern U.S., page opposite, top, may be linked to their habit of using snuff. Other clues show up when comparisons are made between patterns for males and females or white and nonwhites. For example, higher lung cancer rates among men in the northeast and along the Gulf coast, page opposite bottom, are missing in comparable map for females. Occupational exposures, particularly to asbestos, may account for the differences. Patterns for stomach cancer, bottom left, vary among whites and nonwhites. Nonwhite map shows "hot spots" in New Mexico and Arizona, coinciding with high rates among Spanish-Americans who live there. High rates also seen among blacks living in southern Louisiana may be related to diet of hot, spicy, foods. Stomach cancer rates for whites are high in rural counties of north central U.S. Persons of Scandinavian and eastern European descent live there. Unlike some migrant groups who adopt lifestyles of their new country, some carry their own ethnic patterns with them. Predisposition to stomach cancer could be either genetic or result of life style factors. Once various theories for cancer risk are generated, the real work of testing those theories is begun.



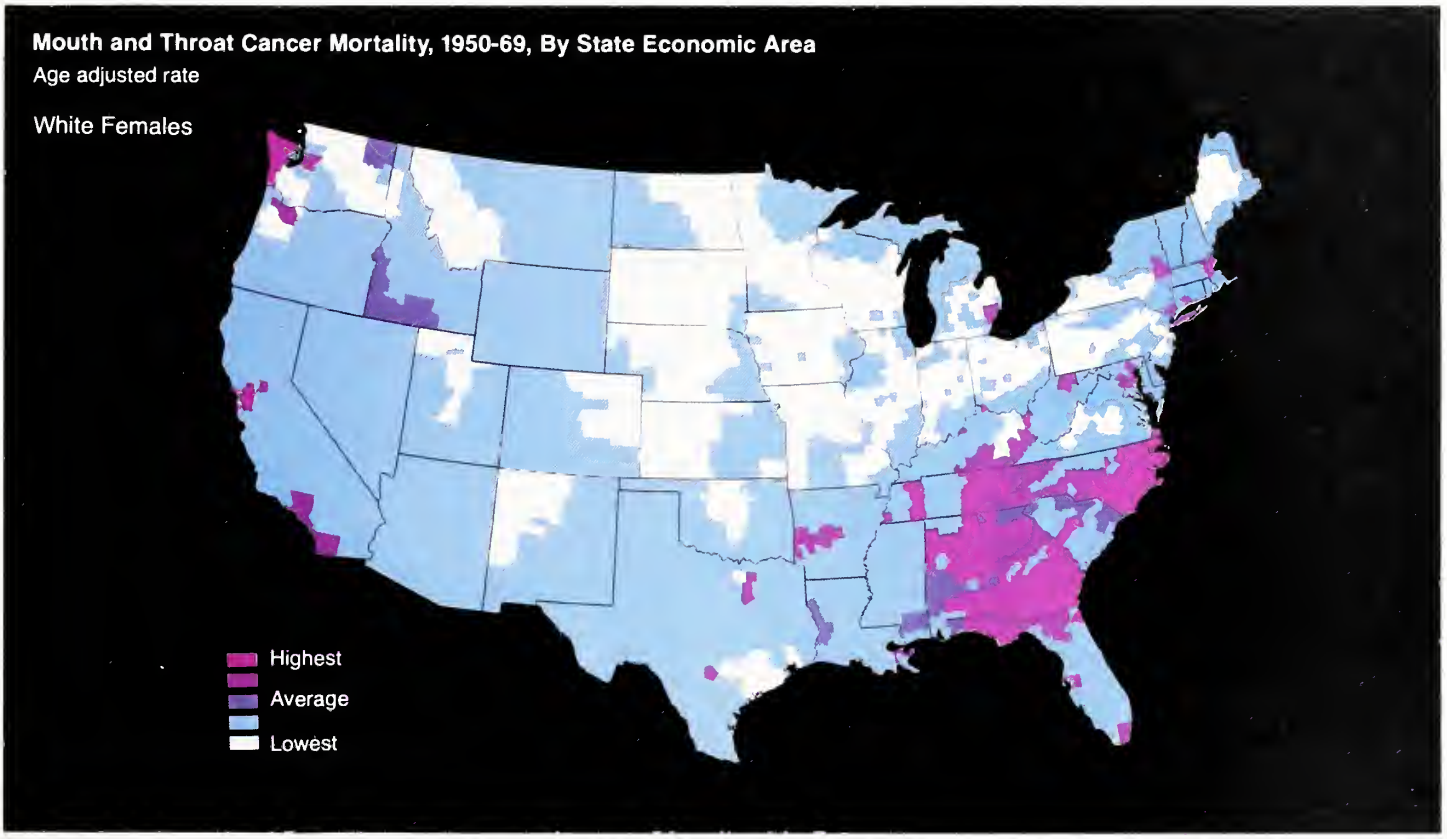
new set of clues to work on."

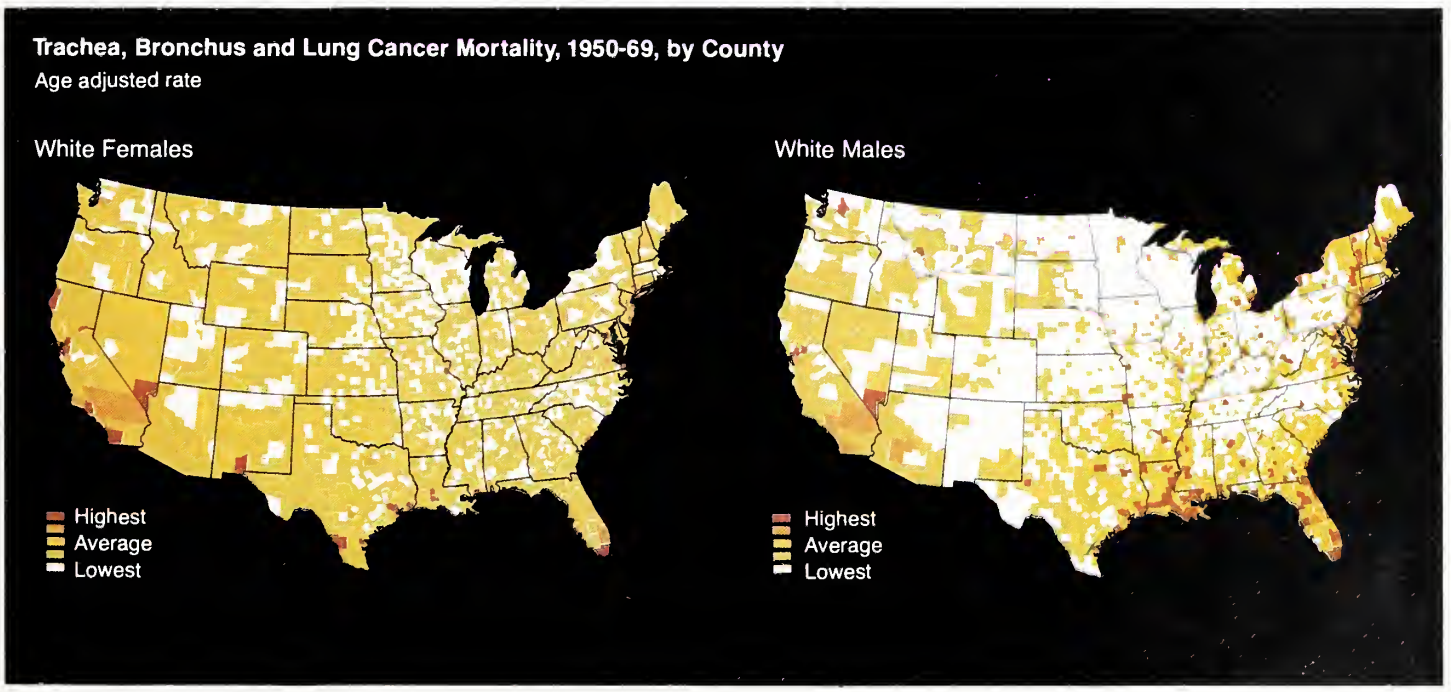
The SEER program generates information about cancer incidence, as well as mortality. The number of new cases each year of a given cancer can be derived from these data and compared with an earlier incidence. Survival trends can also be derived from these data.

The SEER network, which covers about 10 percent of the population of the United States, includes metropolitan Atlanta, Detroit, San Francisco-Oakland, Seattle, New Orleans, plus the entire states of Connecticut, Hawaii, Iowa, New Mexico, and Utah, and the Commonwealth of Puerto Rico.

How useful incidence rates are was demonstrated early in the 1970s by the studies of women who took replacement estrogens at menopause. Almost concurrently, three groups of epidemiologists in California and Washington state reported case-controlled (cases of endometrial cancer matched with control cases without the disease) retrospective studies that established the link: use of these estrogens more than tripled risk for cancer of the endometrium (lining of the uterus). At the same time, this increased incidence of endometrial cancer was seen in the incidence rates noted for those and other states, indicating that the problem was not confined to the women in the study. This rise in the incidence was particularly apparent because the rate had remained stable for almost 30 years.

In response to these findings the Food and Drug Administra-





tion specified that the label carry a warning and urged physicians to give minimal doses with frequent periods off the drug.

Meanwhile, the painstaking followup of clues generated by the cancer maps goes on in a number of locations. "This is a slow, stepwise process," explains NCI's Hoover. "First, we try to correlate high death rates with demographic and environmental data at the county level. At this stage we are trying to raise questions of cause, not answer them.

"The starting point may be an occupational exposure, or it may be a common ethnic and cultural background, or it may be some suspected dietary factor. Then we move on to case-control studies in the high risk communities that will prove or disprove our hypothesis. The goal, of course, is to find ways in which future cancers can be prevented."

One such group of studies is investigating the high incidence of lung cancer seen as "hot spots" along the coastline of the southeastern Atlantic and Gulf states. The first series of studies put the finger on occupational factors —chemical, petrochemical, paper and pulp, and shipbuilding industries. Three areas on the Atlantic coast—where both high lung cancer rates and these industries were located—were chosen for further study. They were Brunswick and Savannah, Georgia; Norfolk and Newport News, Virginia; and Jacksonville, Florida.

"We found that excesses of lung cancer in those areas are related primarily to short-term exposure to asbestos in shipyards during World War II, although cigarette smoking is lurking in the background too," says Hoover.

Another hot spot on the map pointed to the high rates of colon cancer in two rural counties in Nebraska. The increased risk was seen chiefly among people of Czech ancestry and appears to be linked with high intake of fat and dairy products.

Improvements in survival for seven leading sites of cancer shown in bar graph are among data collected by nationwide SEER network of tumor registries, hospitals. Statisticians like John Horm, right, would be lost without computers and printouts because of large volume of information they deal with daily. A new way of showing changes is the "3-D" map, right, developed by NCI epidemiologists. Printed by computer, this map plots age of patients, year and death rate in three different directions. Thus, declines in leukemia deaths that coincide with patients' age, as well as declines resulting from better therapies over the years, plunge sharply from mountain peaks to the deeper valleys below.

Other studies now under way are pursuing workplace risk associated with various industries. The NCI is collaborating with the National Institute for Occupational Safety and Health on 68 projects. In one set of studies NCI scientists, helped by the Oil, Chemical and Atomic Workers International Union, have examined the death certificates of more than 2,000 workers. This has led to the findings of high rates of brain cancer among petroleum refinery workers. The search continues, in the attempt to determine the particular factors involved.

Yet another group of studies is being done of "migrant" populations within the United States. The cancer maps showed that counties in the south have lower colon, rectum, and breast cancer mortality rates than do northern

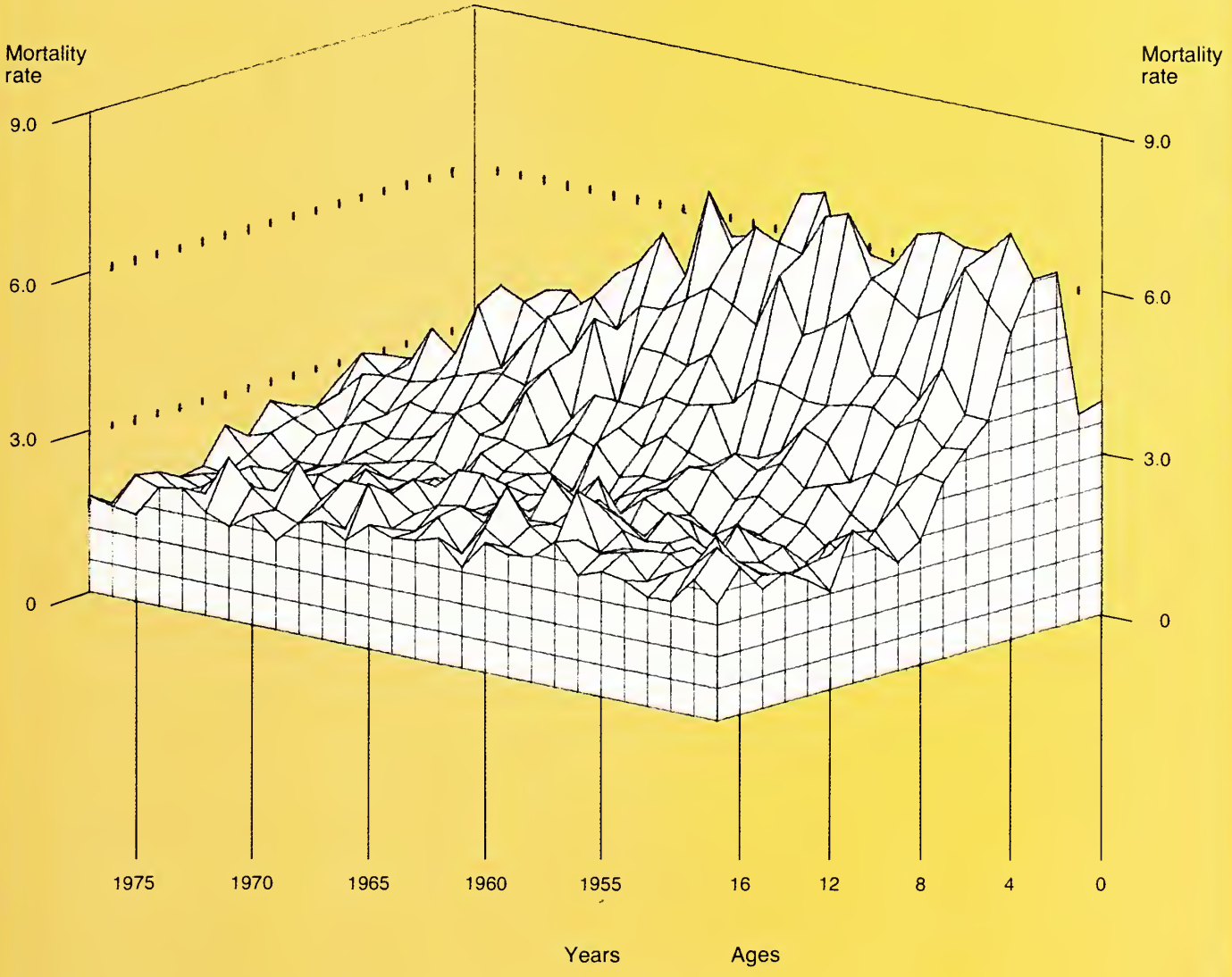
counties. Despite the large number of northerners who retire, or "migrate" to Florida, this area retains the low rates of the south, even among older people.

Studies are planned to identify how much time in the south is needed to bring about the change, whether risk is reduced equally for persons of different age, sex, and socioeconomic class, and whether dietary or other factors are responsible.

These studies will require intricate questionnaires and meticulous fieldwork—the tools epidemiologists use to ferret out underlying determinants of risk.

"We have no lack of clues to follow," says Hoover. "What we need is more epidemiologists who can follow them."

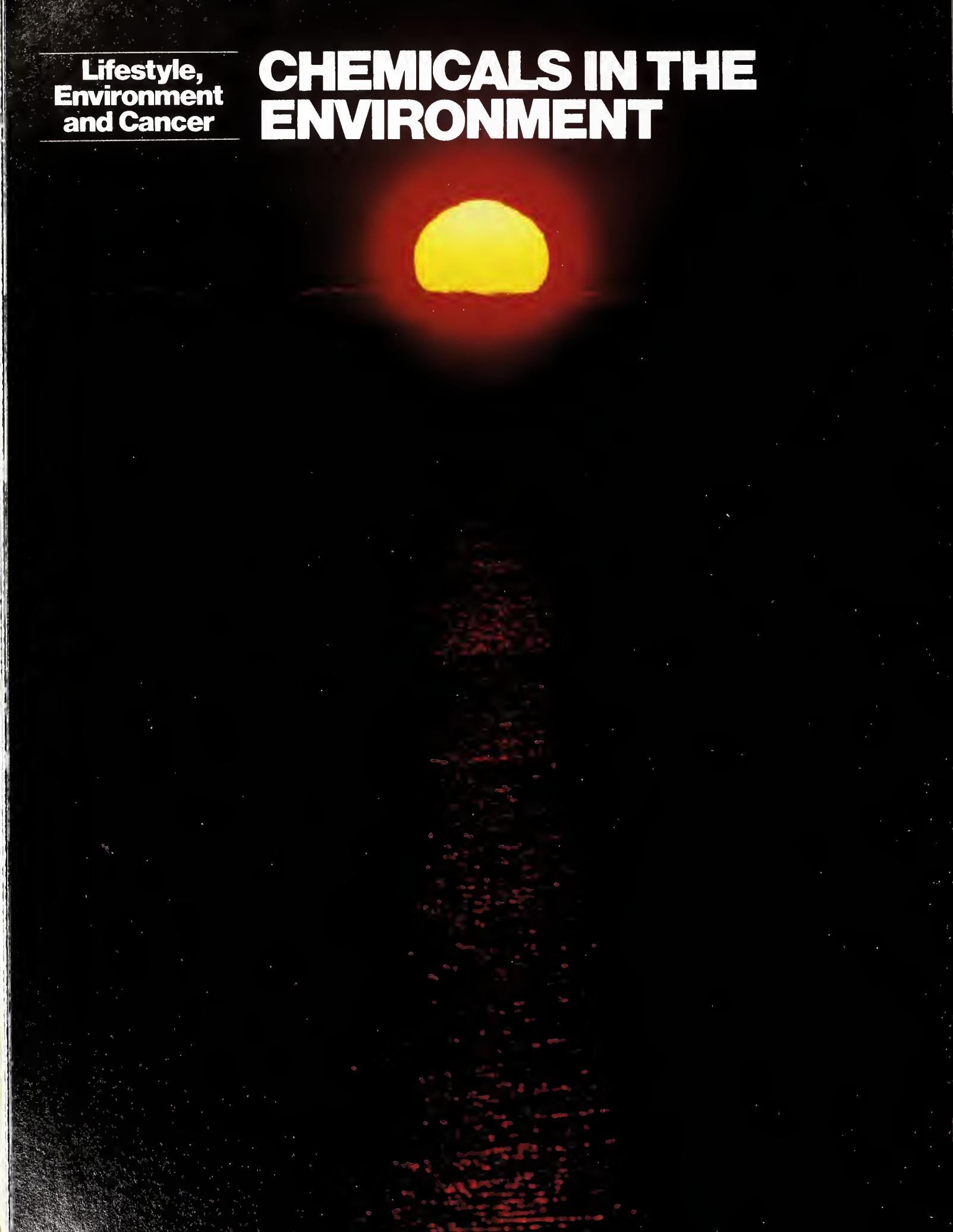
Childhood Leukemia in the United States
Mortality Rates per 100,000 by Age



The Mormons of Utah are one of a number of groups — Aleuts and Seventh Day Adventists among them — being studied for their low cancer rates. Mormons have cancer death rates 20 percent below the U.S. average. Church doctrine prohibits smoking, alcohol, tea, coffee. Large families, such as the one in these pictures, are encouraged. Mormons are not vegetarians; their beef consumption is well above national average. Fewer smoking-related cancers accounts for some of lower rate in Mormons, but rates for cancers of colon rectum and pancreas are also low in both sexes. Mormon women have low rates of cervix, ovary, and breast cancer. Epidemiologists now are exploring many factors, including genetic, to account for low rates. Excellent church records, kept meticulously for many generations, will help greatly.

Lifestyle, Environment and Cancer

CHEMICALS IN THE ENVIRONMENT



The Beaumont works, baking in the unrelenting Texas sun, belies the conventional image of a chemical plant. No noxious odors assault the visitor's nose as they so often do in Niagara Falls, in northern New Jersey, and along the Delaware River. Here, only the faintest whiff of new-mown grass from the immaculate lawn, and the barely perceived fragrance of Texas clay. No black smoke belches from the plant's stacks, only pure white steam that quickly evaporates without a trace. The plant has an air of calm, almost of indolence.

Despite the peaceful appearance, workers at this E.I. du Pont de Nemours & Company plant are manufacturing, among other things, acrylonitrile, a

chemical that has been found to cause cancer in animals and is also a suspected threat to man. It is being produced safely, primarily because an animal testing program that identified acrylonitrile as a carcinogen, or cancer-causing agent, enabled the company to take proper precautions in its manufacture and use. Testing chemicals for carcinogenic activity has become a major component of the effort to reduce the incidence of cancer in this country.

Sometimes it seems as if everything causes cancer. Nearly every day, it appears, new reports indicate this food additive, that pesticide, the other industrial chemical induce cancer when fed to rats. Overwhelmed by the sheer volume of the reports, the average newspaper reader or television viewer is tempted to adopt a fatalistic attitude: There are so many carcinogens in my diet and in my workplace that one more or less will not make any significant difference.

But appearances can be deceiving. Many chemicals have been found cancer-causing in animal tests; but more chemicals have been given a clean bill of health by those tests. Identifying chemicals that are carcinogens is a step toward reducing or controlling exposure to them. In some cases, flat prohibition of use of the chemical is required. But in many others, revised work practices, protective devices, and engineering controls serve to reduce exposure.

Bioassay or testing of chemicals in animals is not new. "It has been going on in an informal manner since the beginning of the National Cancer Institute," says Umberto Saffiotti, now chief of Experimental Pathology at NCI,

Identifying cancer-causing chemicals in the environment is an essential prelude to preventive measures. Umberto Saffiotti of NCI, left, was a principal in developing bioassay format now used in animal testing of potential carcinogens. Tests were first used to evaluate pesticides such as those applied by crop dusters, below. Among 130 compounds tested, DDT and 10 others were found to cause cancer in animals. Workers, bottom, wear protective clothing to clean up chemical wastes abandoned in dumps, a serious environmental problem.

who directed the bioassay program during its early years. At that time, he says, there was no organized program for testing.

"Individual chemicals were essentially looked at on a case by case basis by individual investigators. In the late 1950s, international groups such as the World Health Organization began to recommend that chemicals ought to be adequately tested before they are put into wide use. But those recommendations largely fell on deaf ears."

A major impetus toward increased testing came in 1962: Rachel Carson's *Silent Spring*, in which she portrayed a world whose wildlife had been devastated by pesticides. The book stimulated a sudden public awareness of and interest in the problem of the possible carcinogenicity of pesticides. President Kennedy asked his science advisor to set up a committee to study the need for investigating pesticides. Following that commission's report, NCI embarked upon an animal study—large by the standards of those days—for testing 130 pesticides and related industrial chemicals. The study was done with fairly small groups

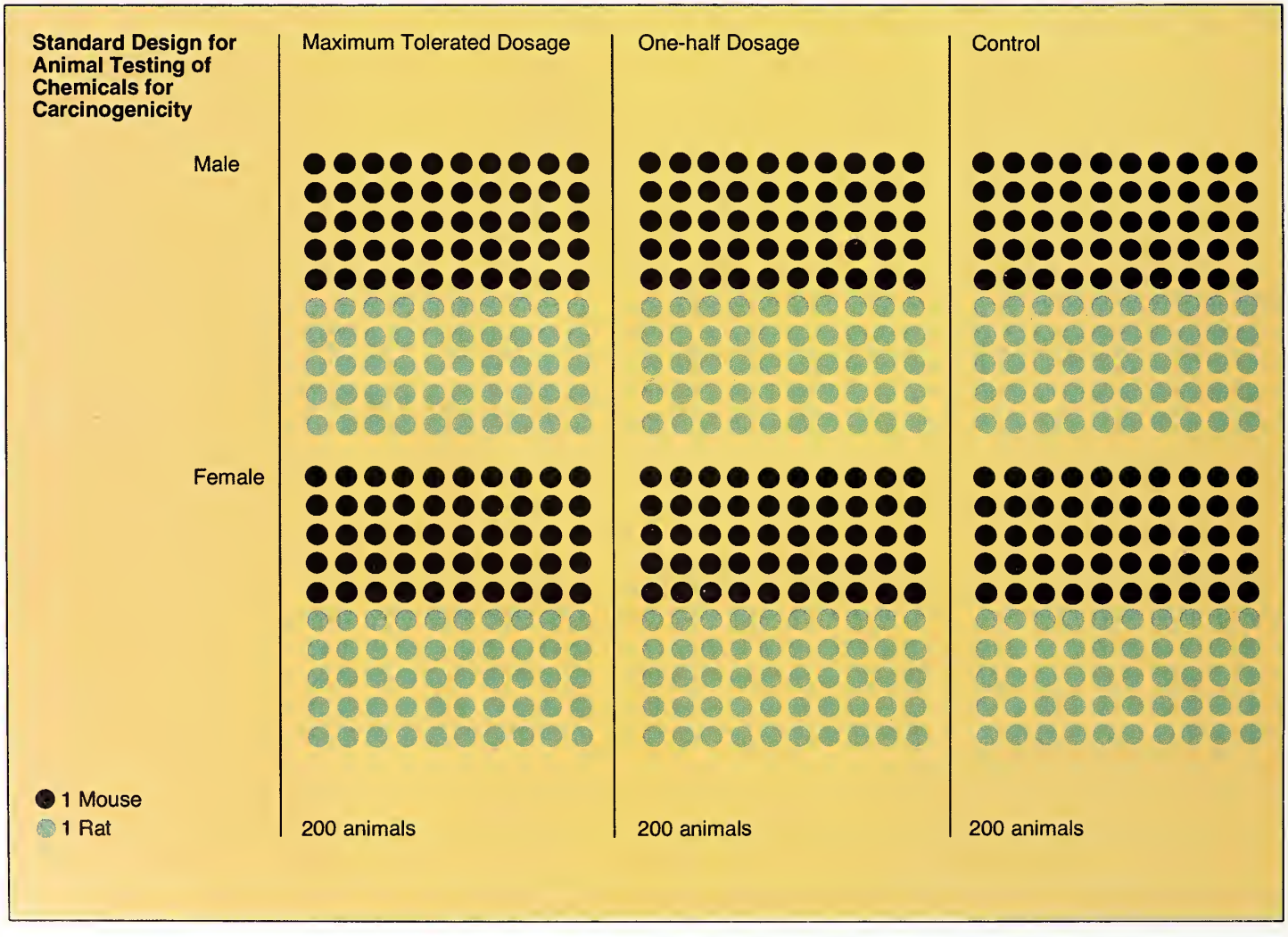
of animals. Results, published in 1969, identified 11 of the compounds—one of them DDT—as cancer-causing agents in animals.

"Not until 1977, when the Toxic Substances Control Act became effective, was there any general law that would require industry to test chemicals for carcinogenicity," says James Sontag, NCI's assistant director for interagency affairs. "But in the mid-1960s, even before the National Cancer Act was passed in 1971, the NCI was planning a large-scale chemical testing program. The pesticide study was part of that effort. But the program increased dramatically after the passage of the Act, chiefly because of a growing awareness of the environment's role in the causation of cancer."

Before such a program could get under way effectively it was essential to develop standardized test methods, or guidelines, so that test results would be consistent, valid, and statistically reliable. Developing guidelines for testing chemicals that would yield results acceptable to the worldwide scientific community was as important a step as performing the tests themselves.

The guidelines state that each chemical should be tested in both males and females of two strains of animals, such as rats and mice. Groups of 50 animals of each sex and strain should be used for each test. When possible, animals should be given the chemical in a form similar to the ways in which humans are exposed, such as by mouth, by inhalation, by skin contact, or in drinking water. Each chemical should be tested at two dose levels: the maximum tolerated dose (which is the highest dose that will not shorten the animals' life span from any effect other than cancer) and a fraction, usually half, of the maximum tolerated dose. Treatment should be continued long enough to produce the maximum response (generally 2 years, the expected

Diagram shows plan for animal testing of chemicals for cancer-causing ability. A minimum of 600 animals is used. Two different species, usually mice and rats, are divided into groups of 50 males and 50 females each. Two hundred animals get the highest dose of test chemical predicted not to shorten animals' life from effects other than cancer. Another 200 receive half that dose. Remainder serve as controls; they receive a placebo. With test evaluation time, each test takes about 3½ years. Elizabeth Weisburger, below, selected many of those chemicals first tested in bioassay program. Selection is now made by committee of government officials.



lifetimes of rats and mice.) Then animals are killed and autopsied.

When all dosage and control groups are added up, it takes at least 600 animals to test each chemical. Each test takes at least 3½ years, and the cost varies from $300,000 to $600,000 per chemical, depending largely on the manner in which the chemical is given to the animals.

Since 1970 the NCI has completed tests on 252 chemicals, says James Huff of the National Toxicology Program, and 105 of these produced tumors in test animals. Another 189 tests are still in progress. Each year a number of new compounds are considered for testing.

The proportion of tests that show carcinogenicity—about 42 percent—does not reflect the share of cancer-causing chemicals in the environment. These chemicals were chosen for testing primarily because they were suspected of being carcinogens. Some scientists think fewer than 5 percent of all chemicals in the environment will eventually be shown to cause cancer in animals.

Worldwide, more than 7,000 chemicals have undergone animal bioassay, though more than half the studies, says Saffiotti, were completely inadequate for their purpose. The National Institute for Occupational Safety and Health (NIOSH) lists 2,700 chemicals that are cited in the chemical literature as carcinogenic, but only about 400 of those have been thoroughly reviewed. The actual number of chemicals that can be identified as animal carcinogens depends on how lenient or how strict one is in accepting the mixed evidence. "I would guess," says Saffiotti, "that there are between 700 and 800 chemicals for which there is reasonably solid evidence of carcinogenicity, and another few hundred for which the evidence is borderline."

According to the International Agency for Research on Cancer (IARC) there are 18 chemicals known to cause cancer in man — and this list includes five industrial processes in which the specific cancer-causing chemical has not yet been identified. Another 18 chemicals are believed to be human carcinogens, though the evidence is less definitive. "There are other substances believed to be human carcinogens, such as alcohol, for which the IARC has not yet evaluated the data," says David P. Rall, Director of the National Toxicology Program.

Epidemiological studies are the only route to determine human carcinogenicity, and it is difficult to establish which factor or factors in the complex human environment could cause cancer. A known exposure to a given chemical in a well-defined group of people, such as industrial workers, can provide the clearest evidence; that is why most of the substances so far identified as human carcinogens are industrial chemicals. Although there are no reliable data, some statisticians have estimated that such chemicals may account for 10 percent or less of all human cancers.

Making animal tests meaningful for man involves two big

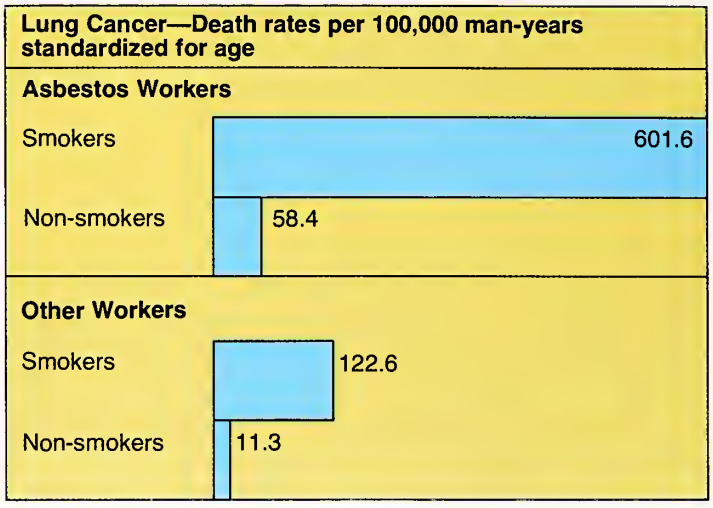
questions: Does the chemical affect the human body in the same way it affects the test animal? And won't the massive doses of chemical given the test animals produce distorted evidence instead of showing what may actually happen to people who are exposed to much lower levels over much longer periods of time?

The first answer: Mice and rats may seem different from humans, but biologically there probably are more similarities than differences. Both rodents and people are collections of cells organized into tissues that undergo the same biological processes and are subject to the same external influences. Moreover, with the possible exceptions of arsenic and benzene, for which laboratory evidence is not clear, all chemicals known to cause cancer in humans are also carcinogenic in animals. Of the 36 chemicals believed to be cancer causing in man, at least 7 — including diethylstilbestrol, vinyl chloride, and acrylonitrile—were first shown to be carcinogenic in animals. Very few scientists now argue that results of animal bioassays are not applicable to humans.

The second answer: There are some valid scientific questions on use of high doses in tests. "But the widespread impression that at high enough doses, virtually any substance can cause cancer is completely fallacious," says Rall. "The majority of pesticides and industrial chemicals tested in animals at the maximum tolerated doses have been found not carcinogenic."

But why must such high doses be used? Primarily to make the tests meaningful by producing measurable effects, and by producing them within the brief life span of the animal, which represents a much longer period in a human life. It is also necessary to detect effects in a comparatively small number of animals, and the effects have to be statistically significant. For example, in a group of 10 animals a chemical would have to cause cancer in 3 or 4 — an extremely potent effect—to provide statistically significant results.

To detect a chemical that will cause cancer in one percent — which would be important in a human population—would require test groups of about 4,700 animals and would be prohibitively expensive. Therefore the NCI investigators developed a work-



There Must Be an Easier Way

Even if it were possible to mobilize all the laboratories in the world with facilities to conduct animal bioassays, it would be possible to test only about 500 chemicals each year. But somewhere between 700 and 1000 new chemicals are introduced into everyday use each year, and an estimated 63,000 already are in use. Faster and less expensive testing for carcinogenicity is needed simply to keep up with new chemicals, to say nothing of reducing the backlog. One promising approach is to use short-term tests that employ microorganisms and cells growing in culture to measure properties thought to be related to carcinogenicity in animals.

One group of short-term tests measures mutagenicity, the ability of chemicals to produce changes in DNA, the genetic material of living things. Since interaction with DNA is believed to be an essential step in chemical carcinogenesis, many scientists believe that most mutagens are potential carcinogens. The best-known of the short-term tests was developed about 14 years ago by microbiologist Bruce Ames of the University of California at Berkeley. He used strains of the bacterium

Best known short-term test for carcinogenesis was developed by Bruce N. Ames of the University of California at Berkeley, who displays a culture dish of mutant bacteria. Another test assays the effects of chemicals on cultured hamster embryo cells, right.

Many workers employed in shipyards during World War II were exposed to dangerous levels of asbestos, a mineral substance known to cause lung cancer in man. Effects of asbestos are greatly compounded by cigarette smoking, left. A worker who both smokes and is exposed to asbestos is even more likely to develop lung cancer than a worker who only smokes or one who is only exposed to asbestos. Evidence from human and animal studies suggest 18 chemicals are capable of causing cancer in man and another 18 are suspected, according to David P. Rall, right, director of the National Toxicology Program.

able compromise of about 400 test animals and another 200 as controls. Using maximum tolerated doses, the scientists estimate they can detect at least 95 out of every 100 carcinogens.

Using high test dosages also helps to balance out some unknown effects, according to Edward J. Baier, formerly of the National Institute for Occupational Safety and Health. Among these are synergism, in which two or more chemicals produce heightened effects in the presence of each other, and cumulative effects, or buildup of chemical effects over time.

Once a chemical has been identified as an animal carcinogen, what happens? Any of several courses: It may be simply banned outright by any number of government agencies with regulatory authority. For example, the Environmental Protection Agency banned the pesticides chlordane, lindane, and DDT after animal tests showed they were carcinogens. The flame retardant TRIS used in children's night clothes was banned by the Consumer Product Safety Commission when animal studies showed it caused cancer. In both cases the regulatory authorities decided any potential benefits from the chemicals were far outweighed by the risk of cancer.

But a chemical may be too important or too necessary for an outright ban. Then the answer may be to severely limit or carefully control its use. This may be the case with the drug reserpine, used to control high blood pressure (hypertension). Reserpine was recently found to produce tumors in test animals. But for some patients with severe hypertension, the risk of death is much greater than the slight and more distant risk of developing cancer from taking reserpine.

Saccharin is another example. Epidemiological studies conducted by FDA and the NCI suggest it may be a weak carcinogen for man, yet consumer pressure has prevented saccharin from being banned outright, as the law required. Instead, FDA put war-

Salmonella typhimurium which are unable to make the essential amino acid histidine. Ames observed that exposure of these bacteria to a chemical mutagen corrects this defect.

Ames, Joyce McCann and colleagues showed that a substantial majority of the chemicals known to cause cancer in animals give positive results, that is, prove to be mutagenic, in the Ames test. The test provided the first indication that some hair dye ingredients and TRIS (the flame retardant used on children's pajamas) are potential carcinogens. The assay costs between $300 and $1000 per chemical and takes only a few days; it is widely used for testing new chemicals.

A second group of assays looks for genetic damage and mutations in colonies of animal cells kept alive by growing them in laboratory dishes where the cells are supplied with all nutrients needed for growth. One such assay detects the efforts of the cell to repair damaged DNA; another looks for changes in the chromosome patterns. Other assays focus on changes that occur when healthy animal cells in culture are transformed into cancer cells. Such changes can be recognized by observing the way cells grow in the culture or by injecting the transformed cells into laboratory animals, where they cause tumors.

Another class of test uses whole organisms instead of live cells. One such assay, for example, looks for damage to a specific gene in the fruit fly, while another looks for genetic damage in cells of a small fish known as the central mud minnow.

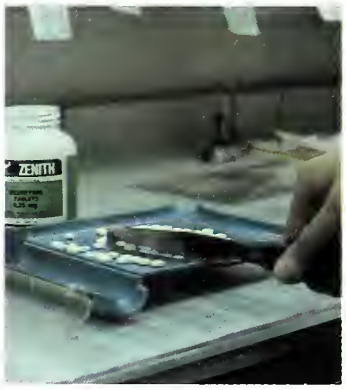
Each test has its own shortcomings. The Ames test, for instance, misses about 15 percent of carcinogens, including chlorinated chemicals and a number of metals. However, these are identified by some of the transformation tests. Most investigators now think the limitation of one test can be overcome by using a battery of four to six short-term tests, perhaps including one from each class of assay. Such a battery of tests would be much less expensive and much faster than animal bioassays, and preliminary studies suggest that a series of tests could detect about 95 percent of carcinogens.

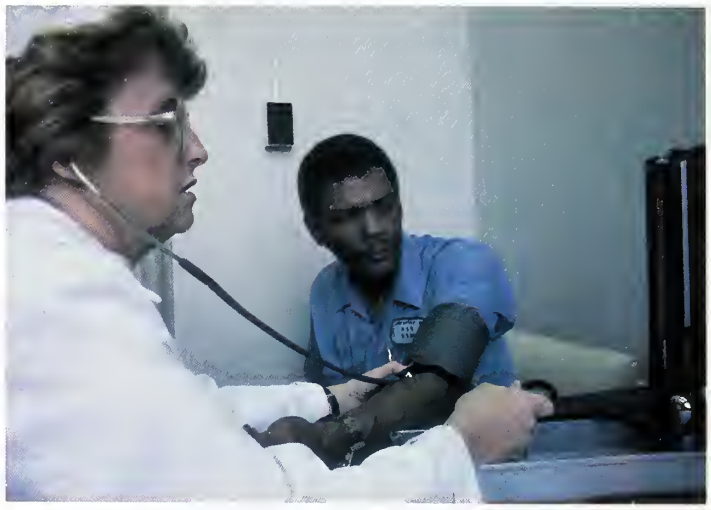
An international group of scientists is now trying to agree on the best series of assays to combine in a battery approach for easier and quicker testing of chemicals for carcinogenicity.

ning labels on products, leaving consumers to make their own decisions regarding saccharin's use.

Acrylonitrile is an example of those chemicals for which potentially hazardous exposure is limited to a fairly small number of people, who can be effectively protected by safety precautions.

Acrylonitrile is used mainly to make textile fibers, and about 1.5 billion pounds are produced in the United States each year. Acrylonitrile is carcinogenic for animals and acutely toxic for both animals and man, producing tremors, convulsions, and paralysis. After it is processed into fibers, it is almost completely inert, producing no ill effects. Although millions of people use clothing made from acrylonitrile, it is estimated that only about 5,000 employees are exposed to it in its hazardous form.





Du Pont's medical director Bruce Karrh explained how the company began its program for control of cancer-causing chemicals in the workplace. When vinyl chloride was found carcinogenic in 1974, industry officials asked whether other chemicals already known to be acutely toxic—such as acrylonitrile—might also be carcinogens. Du Pont and other companies using acrylonitrile worked through a trade association to sponsor animal tests, which were conducted by Dow Chemical Company.

At the same time Du Pont began an epidemiologic study of employees at the Camden, South Carolina, plant where acrylonitrile had been used since 1950.

Results from the animal studies showed that acrylonitrile produced tumors of the stomach, central nervous system, and ear canal in rats. And results from the study of cancer incidence in the Camden employees going back for many years showed higher than expected rates of lung cancer—8 cases among 1,345

How Chemicals Act to Cause Cancer

How chemicals cause cancer is still unknown, but several pieces of the puzzle appear to be in place. Most scientists agree the process involves two major steps; initiation and promotion. A single chemical can act as both initiator and promoter, or two or more chemicals can interact to produce a tumor. First a chemical interacts with a cell, initiating subtle changes that open the door to later malignancy. Other chemicals, not necessarily carcinogenic themselves, then may push through the open door of the vulnerable cell, promoting cancerous growth.

In the early 1940s, Isaac Berenblum, now at the Weizmann Institute in Israel, exposed mouse skin to a single, low dose of benzo(a)pyrene (BP), a carcinogen. He then applied a variety of irritants to the same area of the skin. Many carcinogens irritate tissue, and Berenblum wanted to see whether irritation per se had anything to do with carcinogenesis. Most of the irritants had no effect. However, mustard gas inhibited tumor production and the plant product croton oil greatly increased the number and size of tumors formed. Alone these caused no tumors.

Berenblum realized that although croton oil was not carcinogenic itself, it was playing a significant role in the cancer producing capability of another substance. He called BP the initiator and the croton oil the promoter, and called this phenomenon the two-stage mechanism of carcinogenesis.

Other scientists worked from the observation that the chief characteristic of initiation is chemical reaction of the carcinogen with some component of the cell. Many scientists, including Elizabeth and James Miller of the McArdle Laboratory at the University of Wisconsin, have shown that carcinogens are members of a class of reactive chemicals called electrophiles. The reaction takes place when these electron-deficient chemicals attack electron-rich chemicals within the cell. A few carcinogens are electrophiles in their natural state. But it is one of the ironies of science that most are converted into electrophiles by metabolic enzymes within the body, primarily those within the liver

Continued page 48

Elizabeth C. and James A. Miller of University of Wisconsin's McArdle Laboratory, left, found that most potential carcinogens must be metabolized into a highly reactive form, called an electrophile, before they can cause cancer. Enzymes in the liver not only detoxify some chemicals but convert others to reactive electrophiles. The most likely mechanism for chemical carcinogenesis involves the reaction of the electrophile with DNA, the cell's genetic substance, right. As a result of this interaction, DNA becomes distorted and its genetic code can be misread to produce mistakes that allow a cell to escape normal controls.

What happens once a chemical is identified as a carcinogen? It can be banned by government regulatory agency, or its use may be restricted. Sometimes a substance is too valuable to ban outright. Drug reserpine is used to control high blood pressure, left. For some patients with severe hypertension, risk of death from heart disease or stroke is greater than possible increased risk of cancer from the drug. So use of reserpine may be restricted. Although required by law, banning of artificial sweetener saccharin was prevented by consumer pressure. FDA settled for label warnings on products, leaving each consumer to make personal decision regarding saccharin's use, right.

male workers, with only 4.4 expected. The combined animal and human studies made a serious case for the possibility that acrylonitrile is a human carcinogen.

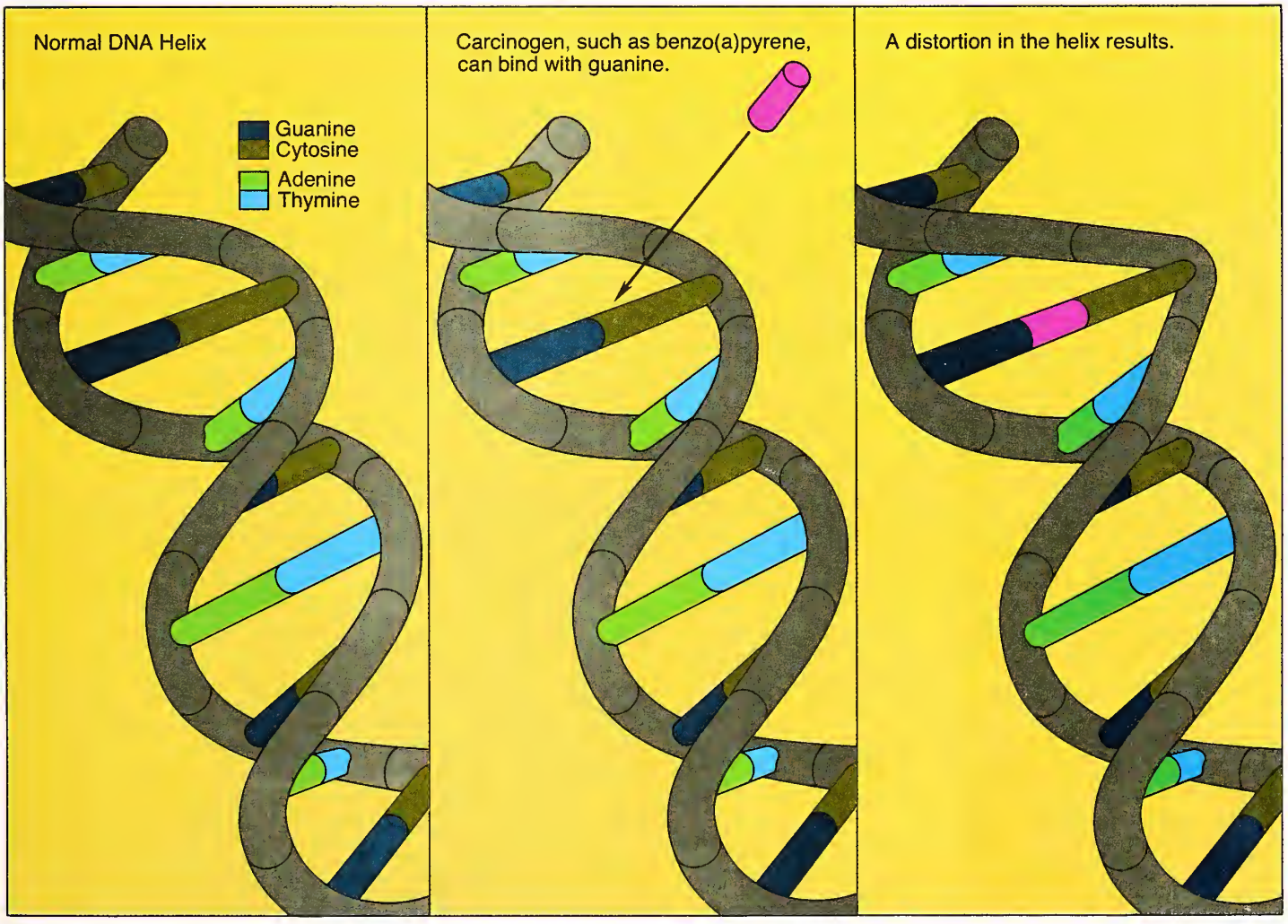
Work began to control exposures. Earlier, maximum permitted exposure was 20 parts per million (ppm) in the air for workers during an eight-hour shift—a safe limit for preventing toxic effects. The company lowered the threshold limit to 2 ppm. Later, the Occupational Safety and Health Administration (OSHA) established a regulatory limit of 2 ppm.

What can industry do to protect its workers from chemical cancer hazards? In Du Pont fiber plants, air flow was increased to remove vapors in some areas. Administrative controls, or changes in work practices, form another safeguard. Workers may work only brief periods, for example, in areas with any possibility of exposure. They may use personal protective equipment such as respirators in areas where vapor is present. "We're operating below the 2 ppm standard," reports Karrh; "in many cases well below it."

"We designed the plant as if we were making cyanide," says C.E. "Bo" Watkins, general manager of the Beaumont works. It was a logical approach; hydrogen cyanide is a by-product of the catalytic reaction that produces acrylonitrile. Levels of acrylonitrile in factory air were well below the permitted 20 ppm level. When the 2 ppm limit was established, only some touching up was needed to lower the concentration.

Portable air monitors found the plant areas with increased exposure. For example, workers who took samples of a batch for testing faced extra exposure to acrylonitrile. Special sampling boxes were built, designed to draw acrylonitrile fumes away from the worker.

Storage tanks are equipped with scrubbers that capture acrylonitrile fumes and dissolve them in water, which is returned to the plant for use as a solvent. Vapors from tank cars being filled with acrylonitrile are returned to the storage tank. In a further



step, tank cars are carefully filled to the correct level for shipping.

Says Bruce Burns, production manager, "Because you can't smell acrylo until it reaches a concentration of about 20 ppm, we put in gas chromatograph monitors." These "sniffers" provide a sensitive measure of air levels of acrylonitrile in various parts of the plant. They run continuously, rapidly detecting any possible leaks or spills.

Employees are an integral part of their own safety control program. All Du Pont workers receive regular physical examinations; people who may be exposed to hazardous chemicals are examined annually. Plant safety rules and chemical handling procedures are emphasized. Says general manager Watkins: "We tell our workers that this chemical is a baddie; we don't want you to get it on your hands, we don't want you to get it on you, we don't want you to eat in this area. Employees are cooperative. They know it's their own health they're responsible for."

Not all plants are like the Beaumont works. If you consider the top dozen chemical companies, says epidemiologist Irving J. Selikoff of the Mt. Sinai School of Medicine in New York City, "then real efforts are being made to control exposure to carcinogens, and often with success. But this probably represents a very small proportion of American industry. Most companies don't even know these chemicals exist, or if they know they exist, then they have no idea that there is such a thing as a carcinogen."

"In many places," adds epidemiologist Phillip Polakoff, director of the Western Institute for Occupational and Environmental Sciences in San Francisco, "control of exposure is done very poorly. There are instances of flagrant disregard for

whose principle function is to break down foreign substances and render them harmless.

The possibilities are that electrophiles attack proteins that regulate some facet of cellular growth, the messenger RNA that carries genetic information from the genes to the cell's protein assembly apparatus, or DNA itself, because all are electron-rich subunits within the cell. Most investigators now favor the theory that the critical attack of carcinogens is on DNA. This theory reasonably explains the existence of the latent period, that lag time between exposure to a carcinogen and the later development of cancer. The latent period may be between 10 and 20 percent of a mammal's lifetime. It is unlikely that changes in a cellular protein or in messenger RNA could be preserved for that long, whereas a change in DNA would be inherited from one cell generation to the next.

Berenblum's two-stage theory postulates that initiator substances cause genetic changes in the cells that occur quickly and are irreversible. Cells can stay in the initiation stage indefinitely if they are not stimulated by a promoting substance to progress to full cancer cells. The theory further states that tumors form only if the initiating electrophile attacks first, before the cell is exposed to a promoter. Promotion can occur months after the initiation stage and still stimulate tumor production.

Complete carcinogens are chemicals, some of which have been identified through animal tests, that can act as both initiators and promoters. At small doses they act only to initiate tumor formation. At high levels they act both to initiate and to promote tumor growth.

The way promotion works is not yet clear, but investigators have observed many cellular effects caused by promoters. The activities of certain enzymes are increased, for instance, and promoters may stimulate an error-prone performance in DNA repair.

Whatever the mechanism of action, it seems likely that promoters in our diet and in our environment are causing some cancers by seeking out cells where initiation already has taken place. John Weisburger and his colleagues at the American Health Foundation in New York City, for example, think that bile acids stimulated by a high-fat diet may promote human colon cancer. E. Cuyler Hammond and his associates at the American Cancer Society long have argued that cigarette smoke contains many promoters that increase the effects both of carcinogens in the smoke and those in the environment.

The theory of two-stage carcinogenesis may explain the high incidence of lung cancer among asbestos workers who smoke cigarettes, according to Berenblum. The incidence of lung cancer for these people is much greater than expected for those exposed to either substance alone or from a simple additive effect of the two substances. The fact that people who stop smoking are no longer exposed to the cigarette's promoters may explain the ex-smoker's progressively decreasing risk of developing cancer. Several investigators have observed that the artificial sweetener saccharin is a promoter as well as a weak carcinogen. And several others have shown that phenobarbital, a commonly used sedative, appears to act as a promoter of liver tumors in laboratory animals. It seems likely that many other promoters will be recognized as we develop a better understanding of the mechanism of chemical carcinogenesis.

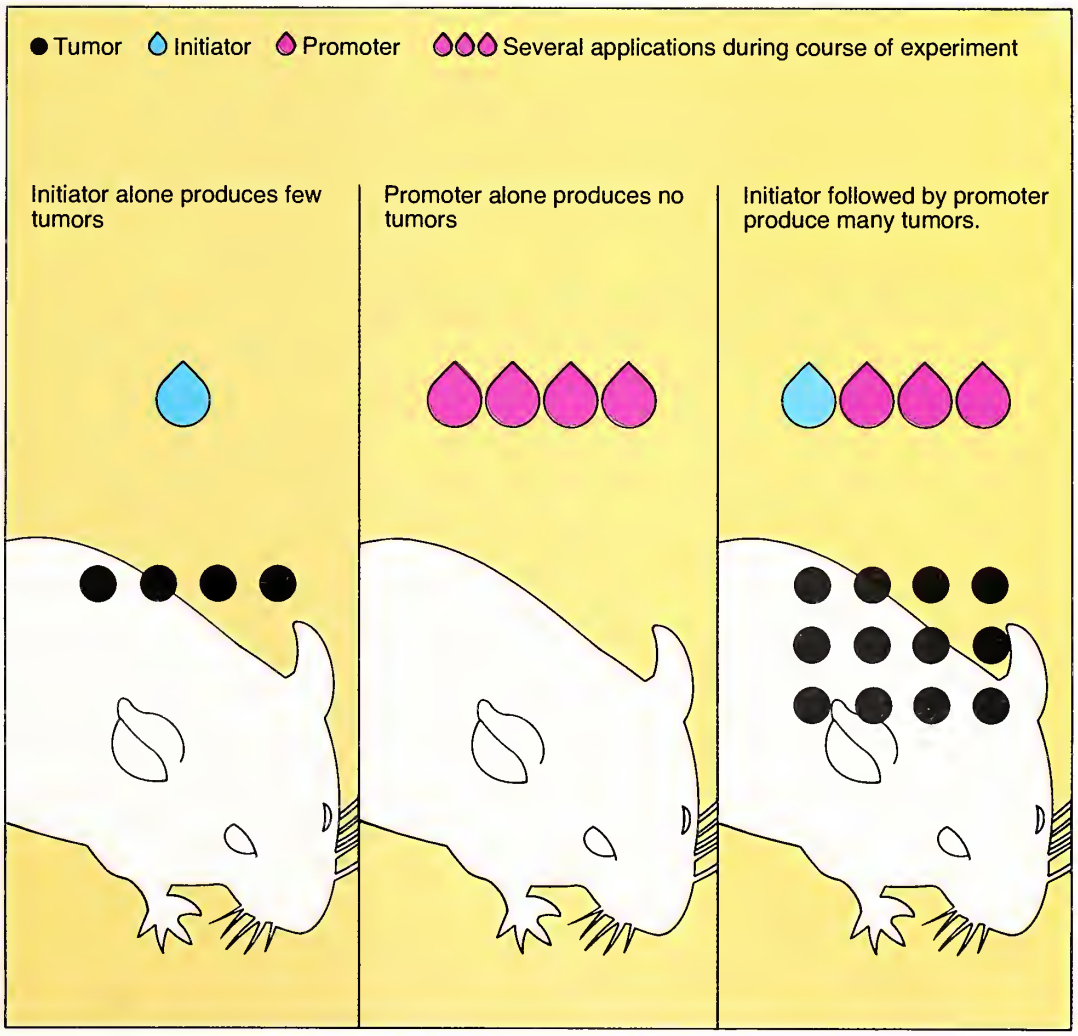
Hazard of carcinogen acrylonitrile, a chemical used in manufacturing textiles, is limited to workers. So at Du Pont's Beaumont works various precautions are taken to limit a worker's exposure to the volatile chemical. Shown at left are two of these: A sophisticated gas chromatograph system, far left, records concentration of acrylonitrile in the air at various points throughout the chemical plant. Employees learn about protective breathing equipment, near left, to be used when they work in areas with any possibility of exposure. New York epidemiologist Irving Selikoff, right, says it's critical to find out which chemicals cause cancer. Then it is at least possible to do something about them.

exposure limits, especially in the smaller industries. There are combinations of chemicals that people are exposed to without the workers, and often even the management, having any idea what they're working with — they're just working with numbers, and they don't even know the names of the chemicals. Medical surveillance of employees," he continues, "usually stops when the employee retires, whereas many of the effects of chemicals often appear after retirement and are never identified."

"Bad faith by management is sometimes a problem," says Selikoff, "but lack of information is more important. We know very little because most of the chemicals being used have never been tested in animals, and even in those for which there are good animal data on carcinogenicity, there have never been epidemiological or human health studies. We have little data on who has been exposed to what chemicals in the past and the extent of such exposures. There is almost no information on dose-response relationships, or how much chemical it takes to have a measurable effect. Yet, according to the Supreme Court, if you don't have this kind of information, there will be resistance to regulation of exposures. We do know that many cancers are associated with exposure to multiple agents, yet chemicals are generally tested one at a time.

"Our knowledge is meager," concludes Selikoff, "but when we have evidence that a chemical is a carcinogen it is at least possible to do something about it. So the critical thing is finding out which chemicals cause cancer. Then the Du Ponts and other companies can take appropriate steps. It's important that not only Du Pont takes precautions, but that everyone who uses the chemical does it too. A guy who works for Company X and is exposed to a carcinogen can be just as dead as a guy who works for Du Pont."

Isaac Berenblum, left, of the Weizmann Institute of Science, Israel, first described the two-stage mechanism of carcinogenesis. He found that certain chemicals could not themselves cause cancer but could greatly enhance the tumor producing effects of carcinogens. Diagram illustrates Berenblum's experiments. When he applied a single low dose of a carcinogen (initiator) to a mouses's skin, the mouse developed few tumors. Other substances, which Berenblum called promoters, produced no tumors when given alone, even though a number of doses were administered. If these substances were applied after the carcinogen, the mouse developed many tumors. How promotion works is not clear, but investigators know the substances cause many cellular changes, which appear to be reversed when promoter is removed. Cigarettes contain both initiators and promoters. Theory may explain high number of lung cancer cases.



Scientists work in their laboratories to discover those differences between cancer cells and normal cells that might be exploited for diagnosis, treatment and prevention of cancer. Our stories in this section focus on two areas of research: studies of the immune system and studies of viruses associated with cancer.

The thought that the immune system might play a role in cancer arose when investigators noted that cancer cells cause the body to mount an immune response, calling in an array of cells to fight the invader. During the 1970s, immunologists faced a major challenge in defining the different types of cells of the immune system. Meanwhile, virologists were searching for the elusive human cancer virus. That search has turned up some surprises about the relationship of viruses to cancer in animals.

In parallel with the investigations, scientists witnessed the birth of two new technologies that changed biology into a new kind of science. With hybridoma technology scientists can grow cells in the laboratory that make pure antibody in large amounts. These substances are critically important reagents for research on the immune system. Recombinant DNA technology was born in 1970 with the discovery of the first of many restriction enzymes. These enzymes allow scientists to splice genes from animal cells and grow them abundantly in bacteria. Now it is possible to actually "see" genes and to learn how they function. The full potential of these techniques has not yet been realized, but it is fully expected that their impact on the field of biology could be as important as the impact of transistors on the field of communications.

We have come a long way in basic research on the nature of the cancer cell, but there is still a long way to go. For all the new technologies and insights gleaned over the past decade, the living cell remains an exceedingly strange and mysterious structure, a challenge to scientists of this and future decades.

III.

Nature of the Cancer Cell

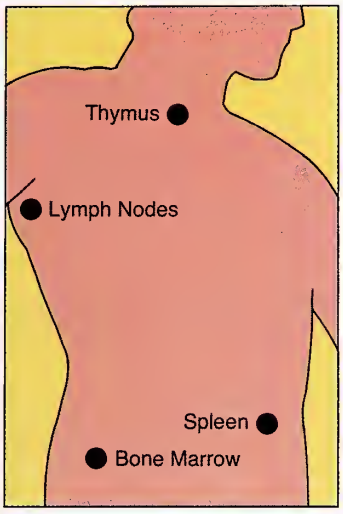
Nature of the Cancer Cell

IMMUNOLOGY: LEARNING THE RULES OF THE GAME

The special molecules, cells, and organs making up the body's immune system have often seemed a hopeless jumble of bits and pieces, toys and games, belonging to an otherwise fascinating collection. Gradually, however, the rules of the game are being established, and some of the pieces are being put into rightful order. Key organs of the immune system, left, include the thymus, the spleen, bone marrow, as well as the network of lymph glands found throughout the body.

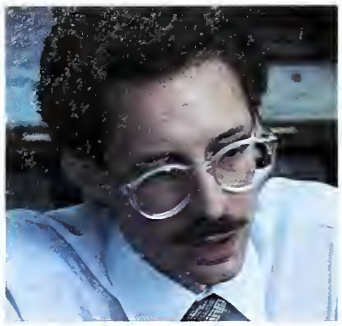
Imagine a child opening a carefully wrapped, oversized birthday package and finding in it thousands of the bits and pieces of many, many games — some familiar, some never seen before — all thoroughly mixed together. Checkers, chess pieces, jacks, tinker toys — they're all there. Before the child and his playmates can begin to enjoy this jumbled birthday gift, they face the monumental task of sorting and organizing the pieces and figuring out the rules of the games.

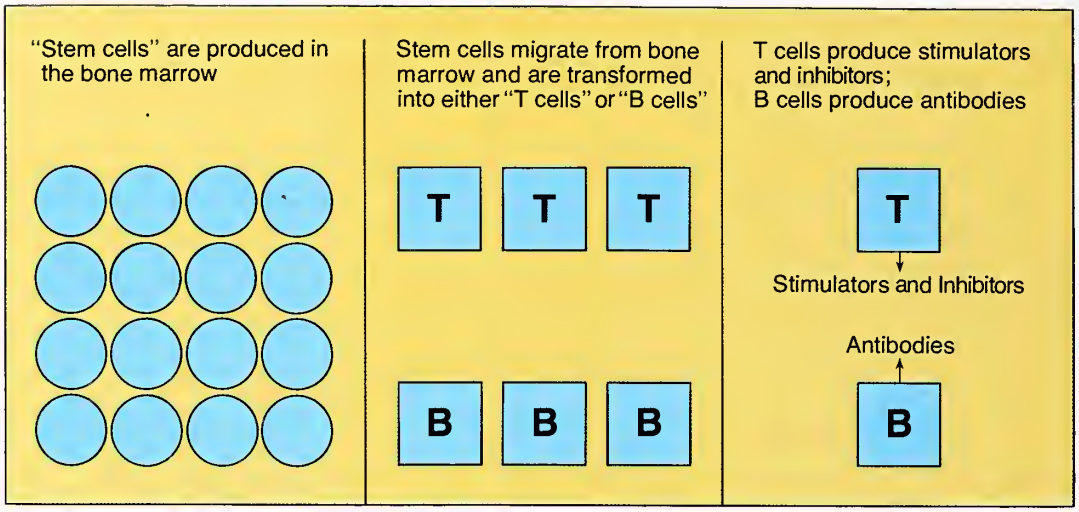
Immunologists have faced much the same task in studying the body's defense mechanisms, its complex system for withstanding infections and combating diseases including cancer. During the past decade, scientists have been figuratively shaking out the bits and pieces of the body's immune system for closer scrutiny. They find an enormous array of highly sophisticated pieces and, persistently, have been putting them together, trying to establish the basic rules of the game. And though most scientists are excited with the progress they have made, they also are awed at the task that still lies before them.



The immune system is without a doubt one of the most complicated of organizations within the body. The body itself is a citadel under constant siege. Its billions of cells are subject to frequent outside attack from invaders such as viruses, bacteria, and other microbes. And from within, there is the paramount threat that normal, healthy cells somehow may be converted into uncontrollable cancer cells, trying to push their way into healthy tissues to destroy normal functions. Some immunologists believe that the same system that helps to withstand foreign invaders also stands vigilant to prevent and combat cancer. But the rules for fighting those different battles aren't the same, nor are the parts of the immune system that must wage those battles quite the same. This growing realization gradually has changed the strategy of the immunologists' assault on cancer for reasons that now seem inevitable.

The body's immune system contains diverse molecules, including antibodies and hormone-like stimulators, many kinds of living units called cells, and an overall programming that is extremely complex. Perhaps the most outstanding cellular components of the immune system, making up much of its bulk, are called lymphocytes. These fall into two main categories—the B lymphocyte cells that make the specialized molecules called antibodies, and the T lymphocyte cells that work by killing invading cells and sometimes tumor cells directly. Scientists estimate that the body contains more than one million million lymphocytes and that about one percent of them are replaced daily. It's no wonder that immunologists find it difficult to keep track of these cells, let alone to figure out what they do.





But it's not the sheer number of cells that's so bewildering. It's more a matter of how many types there are that has been such a challenge to immunologists. And recently, the more immunologists have looked, the more types they have found.

The analogy to games illustrates this challenge. Checkers, for example, is a readily learned game because it has so few pieces and only very simple moves are allowed. However, the same checkerboard may be used with chess instead of checker pieces, multiplying the types of pieces and the kinds of moves many times, thus making the game considerably more difficult to master.

For immunologists, the task is more difficult, by far, than either checkers or chess. They must learn not only what each new piece of the immune system is doing but also must formulate and reformulate their understanding of the rules of the game as they go along. For the immune system contains a vast stock of newly discovered components that still are being categorized. The work is painstaking and involves an assault on often esoteric problems. But most immunologists are convinced that the key to using the immune system to fight cancer lies in understanding how the whole system works.

That belief has been strengthened consistently. For example, a

Monoclonal Antibodies: Trained to Tag the Enemy

The body's immune system is a command network that can summon a molecular attack force including macrophages, natural killer cells, white blood cells and other substances to disable or destroy alien cells which can include cancer cells.

Just since the mid-1970s has a new entity—monoclonal antibodies—fairly burst onto the scene with promises to answer hundreds of longstanding problems in immunology, leading to clinical applications in diagnosing and treating cancer, as well as many viral diseases and immune disorders.

It all started when research scientists Cesar Milstein and Georges Köhler at the Medical Research Council laboratories in Cambridge, England, sought to fuse two different kinds of mouse cells to see whether the different parts of antibody molecules from each kind of cell would mix. Antibodies are protein molecules, part of the immune system's arsenal against foreign substances often called antigens. They usually work by binding tightly to a particular foreign substance

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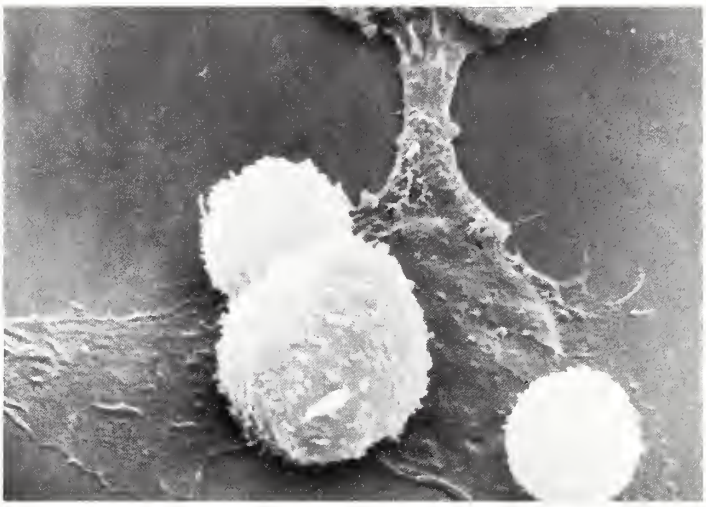
Cells that make monoclonal antibodies are sorted and grown in wells, left. Researchers analyze the products of those cells before selecting the most promising cultures. Monoclonal antibodies are highly specific; those at far right label human breast cancer cells.



Rockefeller University's Carl Nathan, far left, has seen how macrophages, right, cells of the immune system, can sidle up to, surround and then engulf and destroy cancer cells. Seemingly simple, that process actually may be under complex controls to various kinds of cells, left. Among functionaries are cells produced in bone marrow. Some become T lymphocytes that secrete stimulators and inhibitors. Others become B cells, whose main task is to manufacture antibodies.

whole array of cells besides the T and B lymphocytes has been discovered within the immune system. Without doubt, these other cells play important roles in how the body deals with cancer. Some of these have been given exotic sounding names. Macrophage, for example, means big eater. Others, such as killer cells and natural killer cells, have names whose significance is instantly obvious to anyone. All of these cells can kill cancer cells under certain circumstances. Immunologists are trying to understand this killing ability more completely with the hope of harnessing it to benefit cancer patients.

The task is not proving to be easy, again because the immune system is more complicated than it looks at first glance. The cells that can destroy tumors are orchestrated—and can be deactivated—by still other cells of the immune system. Thus the presence of an actively growing tumor may signify that macrophage and killer cells are being restrained or have been turned off through a process that's not fully understood but that involves other parts of the immune system. Immunologists are getting closer to understanding just how the immune system seemingly subverts itself to the benefit of the cancer and the detriment of the body.

Take macrophage cells, for example. They swarm up to foreign cells and can kill by engulfing them. Macrophages also can let loose a whole broadside of chemicals—enzymes, hormones, prostaglandins, hydrogen peroxide, and other factors—to destroy their target cells. Macrophages

are powerfully destructive scavengers. Although they have this deadly assortment of cell-killing strategies, macrophages can be rendered harmless by other cells of the immune system. And though this keeps macrophages from being utterly reckless killers and probably prevents them from wreaking havoc with healthy cells in the body, it also means that macrophages aren't particularly reliable for killing cancer cells.

Cancer destroying cells, including macrophages, apparently serve several master cells simultaneously. Control is exerted by a mix of chemical signals from the various master cells. The code for those chemical signals and countersigns can go as follows: First, a T lymphocyte cell of the immune system responds to something abnormal —in this instance—a cancer cell. The T cell then releases a particular molecule, or factor, directed at macrophages in the body. Quickly they respond to the factor—they stop moving and congregate near where the T cell and tumor are face to face. And, much like a bully that flexes his muscles before a fight begins, the macrophages swell and flex while, inside, their chemical arsenal is fortified. At about the same time, the macrophages release a chemical signal to the T cells, asking them to call in still

in the body, "tagging" it, as it were, alerting other cell functionaries such as macrophages and killer cells to destroy and remove the antibody-tagged invader.

Scientists needed specific antibodies, pure and uniform, in order to take aim at specific antigens. In the natural immune system, literally thousands of antibodies are present. Separating out a single type of antibody has been difficult. And when scientists have succeeded, the quantity of antibody has been uselessly small. The British research team found that by fusing two kinds of mouse cells, antibodies of remarkable specificity could be made. With cloning techniques, they could produce an endless supply.

The two cells forming the original efficient partnership were a lymphocyte from the mouse spleen, which makes a specific antibody but cannot be grown in the laboratory, and a mouse myeloma (cancer) cell, which has lost its ability to secrete antibodies but grows readily in the laboratory. The fused cells are often called hybridomas. They can be coaxed into churning out indefinite quantities of pure antibody. And with steadily improving methods, clever new sorting techniques, and a bit of luck, scientists are finding they can construct hybridomas to make almost any antibody imaginable.

It's a powerful technique. Among the tasks so far being assigned to monoclonal antibodies are: sorting brain cells according to their function and chemistry; isolating important molecules made by gene splicing technology, such as interferon; and characterizing, or mapping, the surface anatomy of normal and cancer cells.

Moreover, monoclonal antibodies are resurrecting hope for some clinical strategies that had been abandoned for lack of antibodies specific enough for the purpose. For example: a tumor possessing a particular antigen can be tagged with monoclonal antibody obtainable in the lab. The antibody attaches to the offending cancer cells, marking them for attack by killer cells of the immune system, while healthy cells are not marked or attacked. In addition, some of the antibody molecules may be outfitted to carry potent drugs to kill cancer cells directly, assisting the immune killer cells. Thus cancer drugs would be delivered only to cancer cells, without damaging nearby healthy cells.

Margaret Kripke, far left, of Frederick Cancer Research Center is studying how ultraviolet light—the same light that tans a sunbather's skin—can increase the susceptibility of mice to certain tumors by changing the way suppressor cells work in their immune systems. This "tipping of the balance" in the immune system toward enhancing cancer can be highly specific, according to Swedish immunologist Ingegerd Hellström, right, who is now at the University of Washington in Seattle.

more macrophages, and also eliciting yet another factor that brings in yet another type of T cell.

So far, the process sounds formidable. However, even as the loop of signals between macrophages and lymphocytes is established, another process begins to shut down the attack. "Nobody knows what stops the loop," says Carl Nathan of Rockefelier University in New York who is studying how macrophages attack tumor cells. But current evidence points at particular T lymphocytes called suppressor cells because they can counteract, or suppress, the body's immune response against cancer cells.

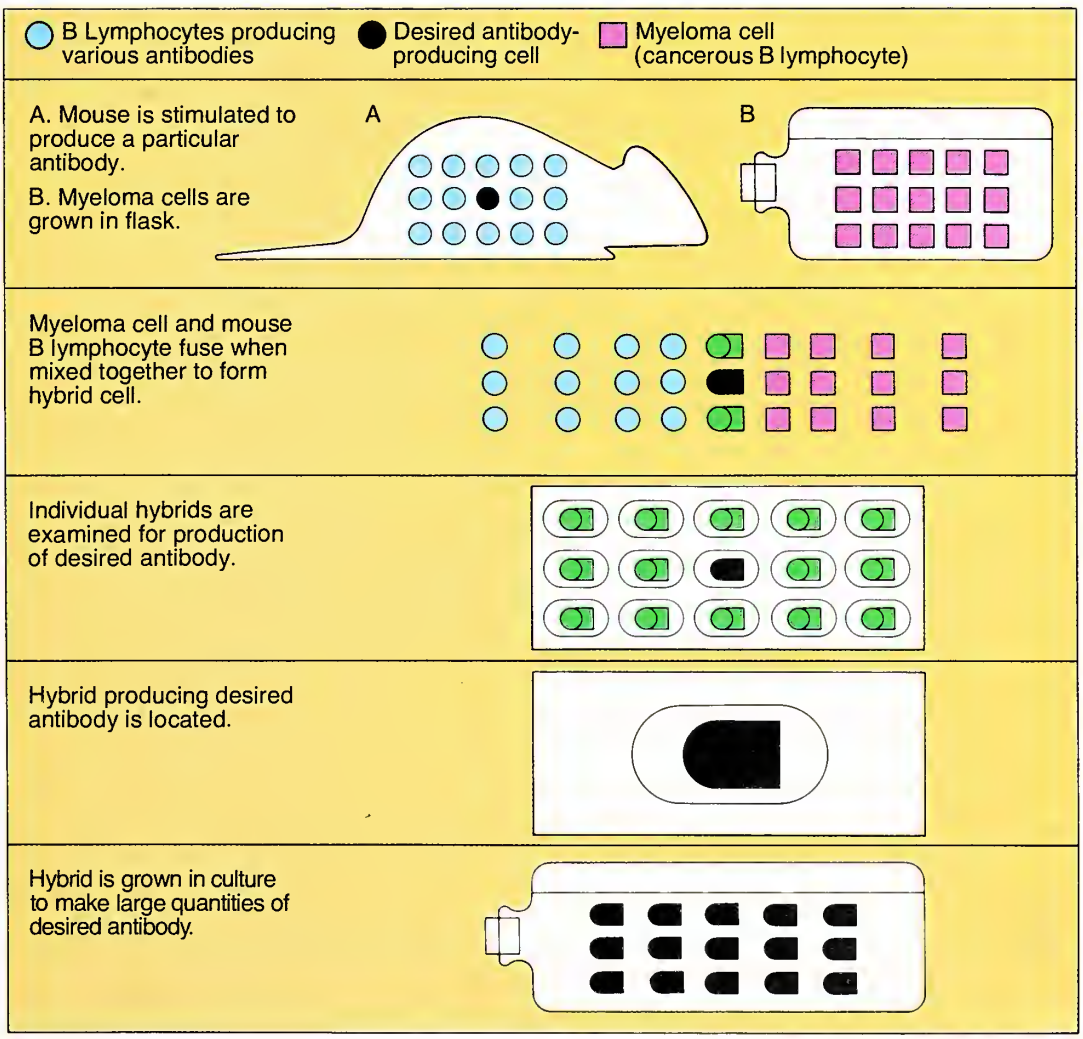
Strategically, there are some really good reasons why the body is endowed with such cells to turn off the immune system. Without them, the system would likely attack anything and everything, including the normal cells that come in its path. Still, the crucial question facing scientists is why the immune system apparently outwits cancer cells much of the time, but loses out to them at others. Here again, the emerging answers are not simple. "No one could have talked in a sensible way about the smoke-screen applied by the immune system before," says Dr. Robert Good, vice-president of Memorial Sloan-Kettering Cancer Center. "Now at least some murky patterns are appearing through the haze."

For one thing, the immune system may home in on its targets by recognizing their "degree of foreignness." The immune system usually has little trouble in disposing of bacteria because they're clearly foreign intruders. With cancer cells, and it seems for some more than for others, the telltale clues can be missing or disguised, leaving the immune system mistakenly disarmed.

Some cancer cells may gain the upper hand by exploiting suppressor cells of the immune system in clever ways. For instance, immunologists Ingegerd and Karl Erik Hellström at the University of Washington in Seattle find that mice with certain tumors will make very specific kinds of suppressor (lymphocyte) cells. Those cells, in turn, make a specific factor that enhances the growth of only that kind of tumor in such mice.

Other examples illustrate the intricate relation between cancer and the immune system, par-

Monoclonal antibodies can be made in unlimited quantities by growing them in bottles, left. First, however, a single cell (lymphocyte) that makes the desired antibody must be selected. Diagram shows general procedure for making these antibodies. Method takes advantage of important properties of two distinct types of white blood cells. One type, obtained from the spleen, produces antibody molecules, while cells of the other type, which are tumor cells, grow readily in culture. When the two are combined in a hybrid, the new cells have both properties—they grow in culture and produce specific antibody molecules.



ticularly the suppressor side of that system. Several researchers, including Margaret Kripke and her colleagues at Frederick Cancer Research Center in Maryland as well as Nobelist Baruj Benacerraf and his collaborators at Sidney Farber Cancer Center in Boston, are studying how the immune system in mice is suppressed to enable cancers to grow. And one thing that brings about suppression in mice is exposure to ultraviolet light, the same light that's responsible for giving sunbathers their tans. Brief exposures to ultraviolet light increase the growth of certain tumors in mice dramatically. But the effect is not due to the direct damage inflicted by the light, which is trivial. Instead, the light turns on suppressor cells in the immune system of the mice, tipping the balance in favor of the growing cancer cells. "No one knows how this regulation works," Kripke admits, "but at least now we have a handle on how to explore the regulatory system."

As with almost everything else in immunology, the regulatory system is proving to be complicated: "Macrophages also are involved when suppression of the immune system sets in after exposure to ultraviolet light," Kripke says. The macrophages no longer act normally. It's unlikely that abnormal macrophages are the kingpins here, although they may carry the message to other components of the immune system that things are amiss.

Unusual, sometimes peculiar looking animals including the nude mouse, below, and the miniature pig, below right, have greatly helped scientists in establishing the rules of the game in immunology. Nude mice, because of a genetic defect, have no thymus and thus cannot make certain cells essential for various immune responses. The miniature pig has an unusually thick placenta that prevents a sow's immune system from influencing that of her offspring. Raised in a sterile environment, such piglets are providing vital clues on how the immune system develops.

To the misfortune of the mice irradiated by ultraviolet light, the message of things amiss is garbled just enough to switch off the appropriate defense mechanisms instead of turning them on. Some scientists speculate that much of the time this switch-off mechanism works in favor of the mice, preventing them from destroying their own skin after minor damage from ultraviolet light.

These same rules apparently apply as well to other cells of the immune system that by themselves are inadequate against a virulent tumor. For instance, under certain circumstances, killer cells and natural killer cells

can destroy cancer cells. Killer cells, which belong to the lymphocyte family (group), act only under the guidance of special protein molecules, called antibodies, that are made by still other cells of the immune system. Antibodies are highly specific molecules that, in some situations, can pick out particular features of cancer cells. If that process of recognition does not take place, killer cells pass by cancer cells, as if blind. And that recognition process can often be foiled.

Natural killer cells may be a bit less choosy than killer cells, and some scientists believe this is because natural killer cells represent a more primitive side of the immune system. Whether natural killer cells require antibody molecules to guide them is an open question. Other important questions also are unanswered: How do natural killer and killer cells differ in other respects? Can these cells be turned on at will to combat tumor cells? No one yet knows. But only a few years ago, these cells had not even been identified.

Other recent discoveries complicate the picture still further. An entire set of inherited traits, carried on what are generally called the immune response genes, play an accessory role in controlling the immune system's activities. So far about 50 such factors have been identified, but they may be a small fraction of a much larger set. They help to determine how effectively the immune system will respond to particular stimuli, such as cancer cells. But the exact way in which they work isn't known.

Along with the inherited part of the immune system comes an even more uncanny part—what can be considered the "instructional" side of immunity. Cells in the immune system learn to tell other cells apart. This is part of their knack for recognizing foreign cells as different from cells belonging to the body. This is really just a restatement of the crux of the cancer and immune system problem. The immune system, which is equipped to make extremely fine molecular distinctions, fails to do so with certain cancer cells. Some scientists attribute that failure to the immune system's no longer seeing or recognizing the difference between the cancer cells and normal cells—between nonself and self. Are the distinctions between such cells too slight? Or can the immune system be taught to recognize even slight distinctions?

These questions aren't yielding easy answers. But even so, insights from immunology are being brought into clinical practice with boldness and determination to test every possible new ploy against cancer. These are the same kinds of everyday benefits and spinoffs typically associated with the technology that's come out of the space program. Practical bonuses thus frequently hitch a ride on fundamental research, and basic immunology is no exception here.

Bone marrow transplants, now being used to treat certain leu-

kemia patients, are one such example. The more scientists and physicians have learned about the immune system, the better able they've been to undertake such transplants. The bone marrow is the source of the cells of the body's immune system, and unless the genetic makeup of the donor and recipient's bone marrow is closely matched, a transfer between them will fail. The recipient's own immune system may reject the incoming cells, or the converse may occur. The incoming cells, which include the array of lymphocytes and other destructive components of the immune system, can attack the cells in the recipient, causing severe sickness and even death.

It's simply not possible to do successful bone marrow transplants without properly matching the genetic traits of the donor with those of the recipient. Advances in immunology and in understanding the genetics of the immune system have steadily improved the ability of scientists to make those matches. So far, the critical markers carrying the important genetic signature seem to reside in substances called HLA antigens. An individual's assortment of HLA antigens is determined genetically. Ironically, it also helps to determine his or her tendency to suffer from certain diseases other than cancer. The reason for that association baffles scientists, but it hasn't prevented them from using what they do know about HLA to make good tissue matchups between donors and recipients.

Immunology is working its way into cancer diagnosis and treatment in other ways. For example, some tumors produce characteristic signatures in chemical markers called antigens, that can be identified by sensitive laboratory tests, originally

developed for use in basic immunology. Although these antigens can give false signals about the presence of cancer, they represent one more set of clues to be scrutinized, clues that can help in the early diagnosis of some cancers. But they also can be used during the course of therapy as a guide to effectiveness.

For instance, in China a simple immunologic test, when carefully performed and analyzed, suggests to surgeons that a patient may have liver cancer. After surgery to remove such a tumor, the analysis is repeated periodically to see whether any

Interferon: A New Approach to Cancer

Interferon is a protein molecule made by the body's immune system in minute amounts. The molecule somehow helps the body to combat certain diseases, including those caused by some viruses and possibly also including cancer. Just how well interferon can act against cancer is a question now under intense scrutiny. Though so far only a limited number of cancer patients are receiving interferon, their medical progress is being closely monitored to see how effective interferon may be.

So far only interferon made by human cells is active in man. Currently, the main supply of such interferon is prepared from human blood cells. The difficulties in purifying interferon from large quantities of blood cells makes the cost of clinical trials as much as $30,000 per patient.

However, there now is a good chance that an altogether different way of producing interferon may not only reduce the substance's price substantially but also may make the supply ample for treatment as well as basic research projects.

The new way of producing interferon depends on the rapidly emerging recombinant DNA technology. This technology enables scientists to produce virtually any protein in simple organisms, such as bacteria. These bacteria can be grown cheaply and rapidly, and when properly manipulated can make vast quantities of desirable proteins.

During 1980, several newly formed commercial companies that specialize in the new technology announced that they'd developed microorganisms that could make human-type interferon. Although such interferon lacks certain sugars normally found in interferon obtained from human blood cells, the synthetic variety still shows certain antiviral activity. That preliminary evidence of genuine biological potency keeps alive the hope that recombinant DNA-produced interferon can come into medical use.

"No one could have talked sensibly about the smokescreen applied by the immune system before," says Robert Good, left, vice-president of Memorial Sloan-Kettering Cancer Center. "People overestimated what could be done from where we were in tumor immunology 10 years ago. We had to learn that it wouldn't be quite so easy. It's a matter of learning through systematic scientific inquiry. Someday we'll wonder why it all seemed so complicated."

vestiges of the cancer remain during subsequent treatment. Because that form of liver cancer is associated with a virus-caused hepatitis, it may prove possible to prevent the cancer one day by using the immune system to destroy the virus before cancer sets in.

Immune tests for tumors already are useful for monitoring the effectiveness of treatments, such as chemo- and radiotherapy. Scientists also are developing strategies to use the immune system to deliver drugs directly to tumors, sparing healthy tissue. One such strategy involves attaching a potent chemotherapeutic drug to an antibody molecule that would go specifically to cancer cells. Scientists are working on many variations of this strategy to exploit the tools of the immune system with the hope of destroying cancer cells more selectively than is now possible.

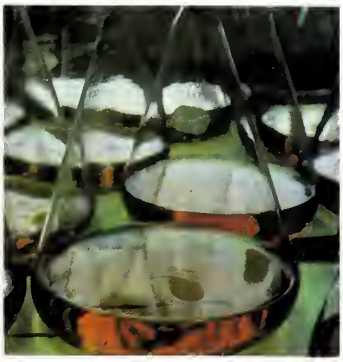
The most daring but perhaps the most desirable therapeutic strategy is to find ways of redirecting what seems to be the immune system's own misguided activities. Somehow the whole marvelous force of the immune system goes awry when cancer cells begin to take over. There's a growing feeling that such an imbalance can be restored in favor of the patient. There's also a feeling among many scientists that unlocking the immune system's strongholds will provide a more natural way of combating tumors, a way that may inflict far less harm to patients than do current treatments.

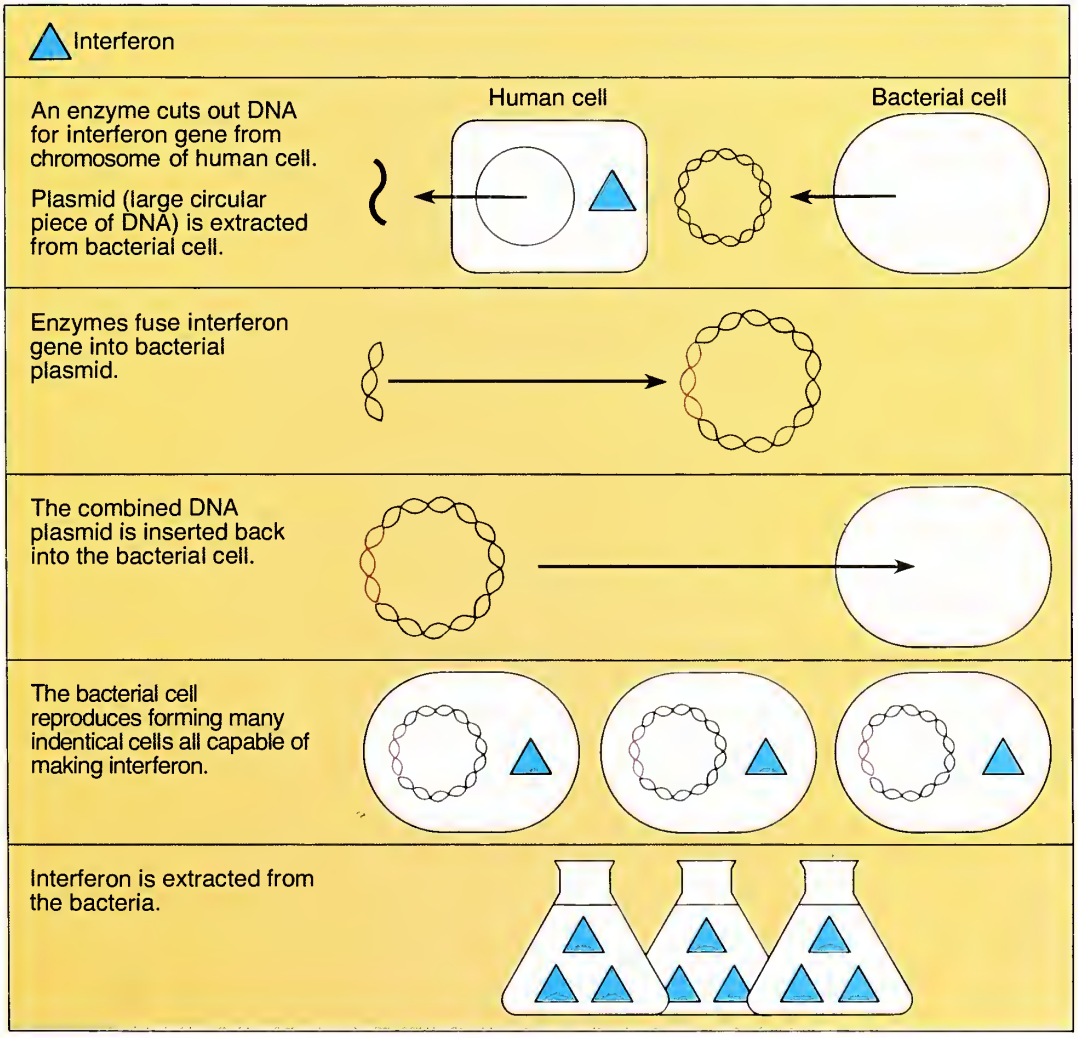
Many immunologists are, if anything, more optimistic and more enthusiastic than they were a decade ago, with good reason. Steadily their basic insights are being put to use to help cancer patients. Although much still remains to be mastered, certain immune-based diagnostic tools are used routinely now for guiding a medical staff in administering certain cancer treatments. And other tools, such as the means for typing and matching tissues from healthy donors for use in cancer patients, are also an offshoot of fundamental studies in immunology.

Sloan-Kettering's Robert Good and others predict that the same success eventually will come for immunology as a means of fighting cancer. "It's a matter of learning through systematic scientific inquiry," he says. "Someday we'll wonder why it all seemed so complicated."

"We need an army of young people testing ideas," declares Good. "There's no dearth of really good problems to be worked on in cancer immunology, and lots to be sorted out," he continues. "People over-estimated what could be done from where we were in tumor immunology 10 years ago. We had to learn that it wouldn't be quite so easy and that clinical applications will take longer."

Conventional means for obtaining interferon involve growing human cells, left. More recently scientists have learned to make interferon in bacteria, growing such microorganisms on simple nutrients in flasks, below. This is made possible by new recombinant DNA technology, right, in which the genetic information for interferon's structure first is taken from a human cell and then placed onto a DNA molecule from bacteria called a plasmid. Put back into bacteria, that plasmid then enables bacteria to make interferon abundantly as the cells grow rapidly.

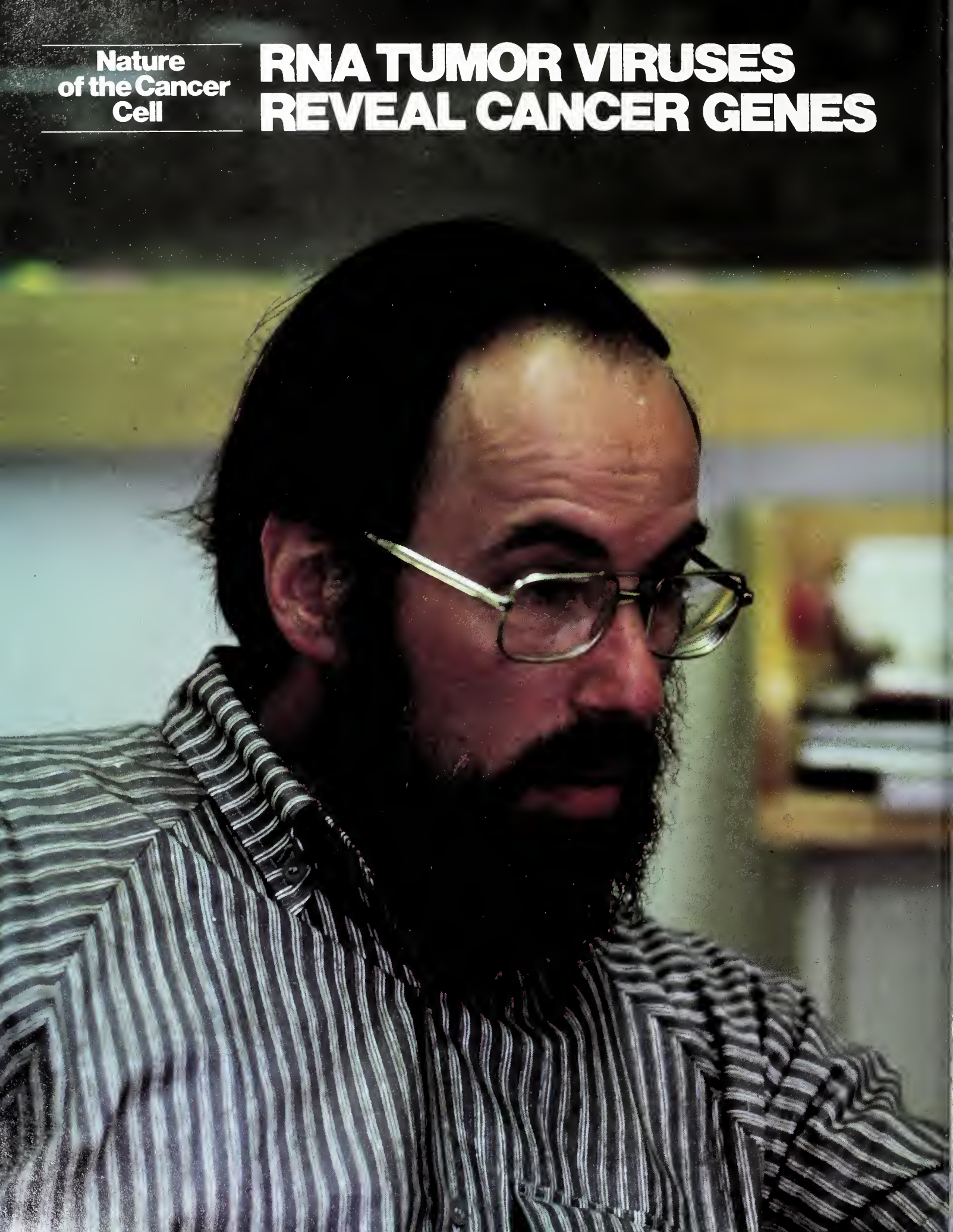




New technologies, such as those shown here, have revolutionized the way scientists can look at the detail of cellular molecules. Gels and sophisticated machines are the more visual parts of the new technologies. But a myriad of restriction enzymes were discovered and characterized in the 1970s. These are responsible for recombinant DNA techniques that allow scientists to isolate genes from the complex chromosomal mass in animal cells and splice them into the bacterial chromosome where they can be duplicated and studied. With enzymes, machines and gels, scientists can read the genetic code, above, in DNA — a feat unthought of in 1970. Knowing that gene code and how it relates to proteins made by the body are important tools for the next decade as scientists continue to explore the nature of the cancer cell.

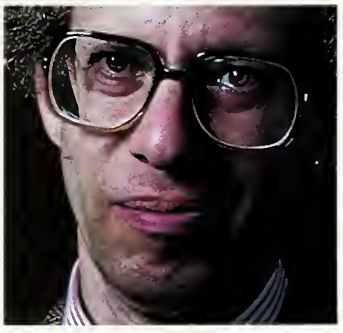
Nature of the Cancer Cell

RNA TUMOR VIRUSES REVEAL CANCER GENES



Do viruses cause human cancer? No one can say for sure, but the notion has persisted for the past decade, coming periodically in and out of fashion.

In some respects, the whole story of viruses and cancer has come full circle during the past few years. For a while, scientists believed that viruses simply invaded normal cells to somehow corrupt them and turn them malignant. Then, for many scientists, a role for viruses in that corruptive process looked unlikely, at least for any known human



cancer. Now those two extreme interpretations seem to be giving way to a third possibility, a kind of compromise: Basic elements of heredity, single genes, may be the principal culprit in the process of biological corruption called cancer. And ironically, those genes, which are a characteristic ingredient of many tumor causing viruses, may also be a normal component of cells throughout the animal kingdom. The question narrows but the puzzle remains unsolved: How can simple genes — found either as part of a simple virus or as part of a considerably more complex cell — act in such a way as to cause cancer?

"Control" is the word that scientists keep coming back to. The gene, the virus, the cell — something gets out of control, and what is normally an orderly process quickly loses all sense of order. A fascinating picture is beginning to emerge from this odd melange — a picture that a few astute scientists began to see taking shape more than a decade ago. But in the meantime, a vast amount of fundamental information was needed before the crucial images could come into focus.

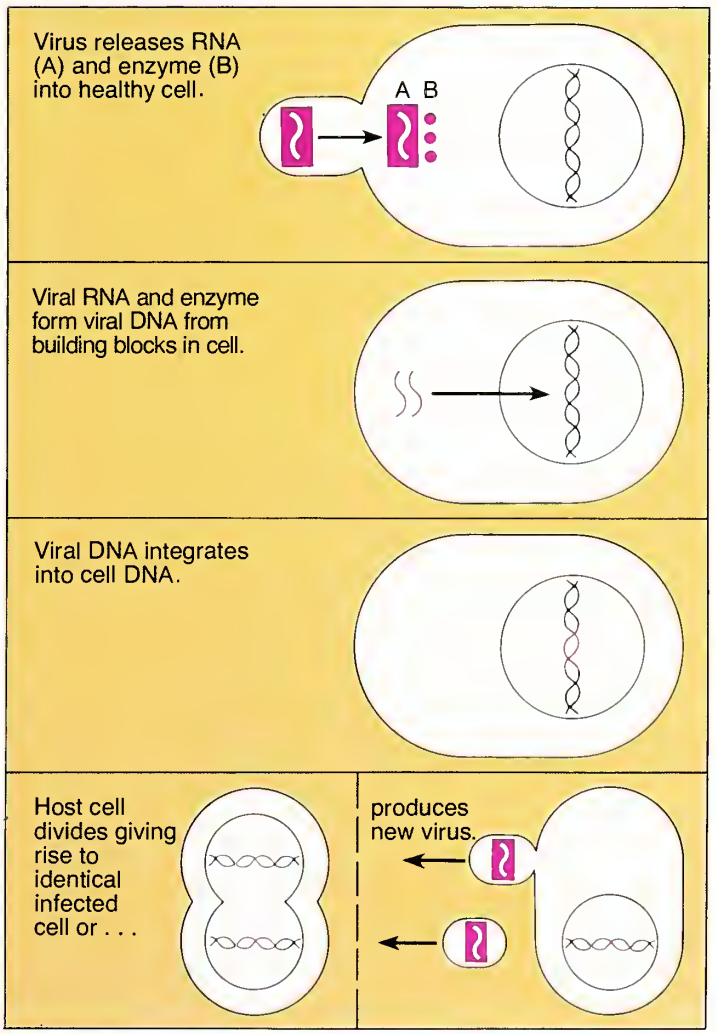
Much of that information has to do with the oddities of viruses themselves. "They are parasites", explains MIT biologist David Baltimore, Nobel Laureate and longtime student of viruses, "and they can't reproduce on their own." That is true for all viruses. But it is a special group of viruses that can cause cells to transform, or in other words abandon their orderly growth and behave in every respect like cancer cells, to which Baltimore and other scientists have turned.

These special viruses often are called retroviruses. Baltimore and Howard Temin of the University of Wisconsin shared the Nobel prize in 1975 for studies related to these viruses. Both were drawn to studying them in part because the retroviruses are chemical oddballs. Instead of relying on DNA to store genetic information as most plants and animals do, the retroviruses use a similar but by no means identical chemical known as RNA. But these viruses still are parasites, meaning they're very much dependent on the biochemical apparatus available to them in the animal cells they invade. Thus, Temin reasoned quite correctly that the viruses needed some trick for plugging their own genetic information into a cell and somehow wresting its control.

That trick is accomplished by a unique enzyme, known as reverse transcriptase. Initially, Baltimore and Temin's discovery of that trick spawned a never realized hope — to trip up retroviruses and thereby prevent cancer by interfering with that special enzyme. Ironically, that same enzyme now is in wide use, and its availability has contributed in a major way to the recent developments known as recombinant DNA technology. This new technology which allows scientists to grow animal genes in bacteria may provide important materials like insulin and human growth hormone. Recombinant DNA technology was never dreamed of when reverse transcriptase was initially but incorrectly seized on as the Achilles heel of tumor causing viruses.

The original strategy — of tripping up retroviruses by interfering with a special enzyme — has been proved too simple or, rather, the retroviruses have proved themselves far subtler than originally thought. For one thing, these viruses don't simply destroy the cells they invade as do many kinds of viruses that cause infectious diseases. Instead, the retroviruses can remain dormant, cleverly hidden within the cell. To do so, the retroviruses succeed with yet another trick: They insert themselves in disguise, so to speak, into the cell's genetic material. Here again, the retrovirus relies on special enzymes to achieve this

MIT biologist David Baltimore, facing page, and Howard Temin, left, of the McArdle Laboratory, Madison, Wisconsin, shared the Nobel Prize in 1975 for their independent discovery of reverse transcriptase. That enzyme now plays an important role in recombinant DNA technology, but in 1970 its discovery stimulated scientists to study how retroviruses cause cancer. Viruses are parasites; they need an animal cell to reproduce, diagram below. Retroviruses carry reverse transcriptase into cells they infect. Enzyme enables them to convert their RNA to different chemical form — DNA — one that cells use to encode genetic material. Retroviruses then accomplish sleight of hand; they sneak some or all of their genetic information into a form that is nearly identical to the cell's own. When inserted at the proper place, retroviruses can cause cells to become cancer-like, growing out of control. Retrovirus may also instruct cell to produce new virus particles, but cell is not destroyed in the process.

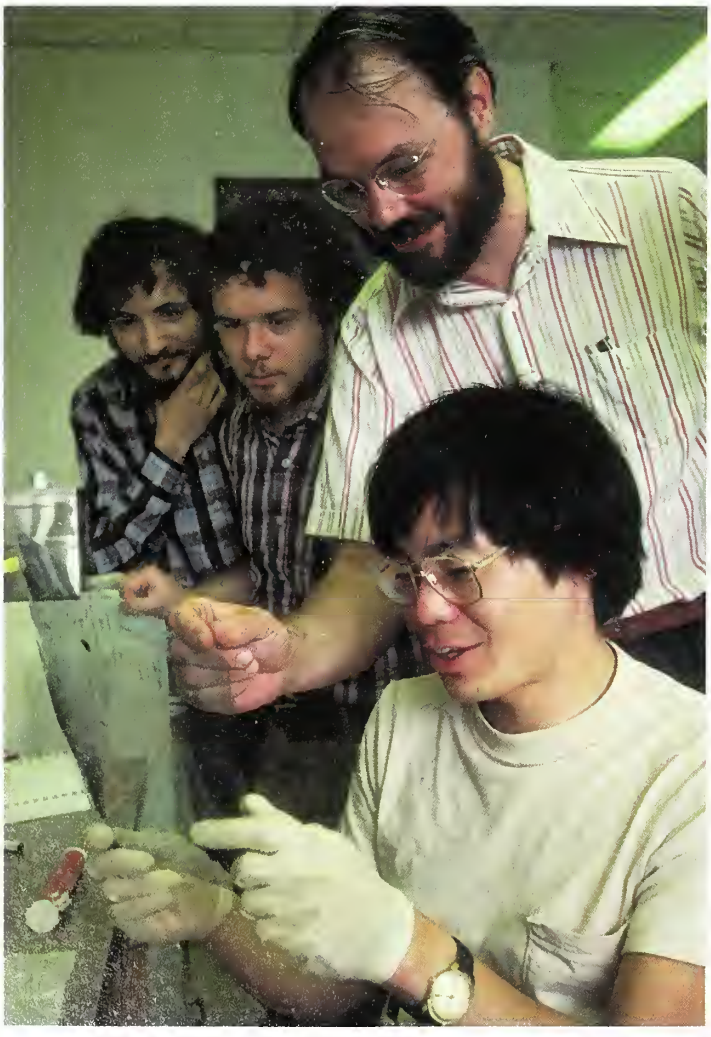


chemical sleight of hand.

A retrovirus can sneak some or all of its genetic information into a form that is undistinguishable from the cell's own. Thus, the virus' genetic information can quietly lie dormant for generations, continuing to coexist with the rest of the genetic information necessary for a cell's life. In this state the virus can be inherited just like other traits such as hair and eye color.

This quiet, unassuming coexistence of virus and cell genes may begin to explain how the delicate machinery that ordinarily regulates a cell's growth can be thrown without warning into disorder. Some of the retroviruses carry a special gene that has come to be known as the *src* gene, named for the sarcoma tumors that it can cause. Peter Duesberg and colleagues at the University of California at Berkely, Peter K. Vogt at the University of Southern California, and Hidesaburo Hanafusa at Rockefeller University in New York City, all showed in the early 1970s that these viruses contain a special gene. Although the experiments required to prove the presence of that gene were rather complex, the conclusion was simple and clear. The experiments involved studying altered forms of the virus called mutants.

"We were studying a virus that had lost its ability to cause sarcomas in chickens," Duesberg explains. Retroviruses have been found in many animals. But they were found originally in chickens by Peyton Rous. The "Rous" sarcoma virus was the first virus shown to cause a tumor, and its discovery brought Rous the Nobel prize in 1966. In the years since 1911, when Rous first isolated the virus, many investigators have sought to explain how it causes cancer.



Genes Occur in Pieces

The study of viruses has contributed enormously to basic biology. But in 1977, it helped spark a revolutionary change in scientists' understanding of how genes direct the synthesis of proteins. That change started when scientists became aware of the unusual way in which certain viruses that cause cancer in animals handle their own genetic material.

Typically, genes are long stretches of DNA. Before a gene does anything in a cell, it usually must be turned into a protein. First, a gene's chemical sequence, which reads like a simple code, is converted into a similar RNA copy or "transcript" of that code before it is "translated" into a different chemical language to form a protein. Such proteins serve a variety of roles in cells. For example, they form necessary structures and act as enzymes to conduct much of a cell's chemical activities. The whole process of turning genetic information into useful proteins is intricate.

That intricacy has an embellishment that turned up unexpectedly in 1977. Traditionally, molecular biologists have studied bacteria and the viruses that infect them. Bacteria grow rapidly. They have no discrete nucleus and their genes are few. In fact, bacteria probably have just enough DNA to code for those proteins necessary for survival. When scientists began studying cells infected by animal viruses, a new revelation was made. Animal cells are overloaded with DNA. Whole long stretches of some genes do not really represent the information for making the eventual protein product. Those stretches in fact are cut out before the protein ever gets made. In the process, the intermediate RNA (often called the transcript) must be cut and spliced to reduce its size and remove the extra material. Such genes are known as "split genes" and the extra material is called "intervening sequences.

The full significance of this discovery is yet to be realized. However,

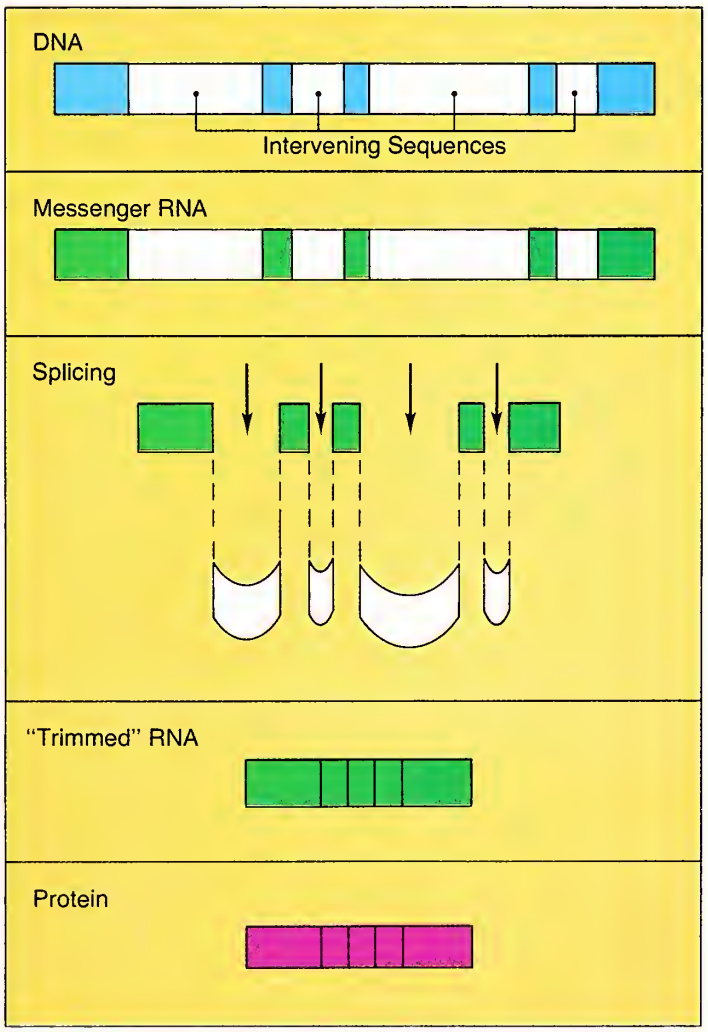
Peter Duesberg, near right, of the University of California at Berkeley, and Hidesaburo Hanafusa, far right, of Rockefeller University, conducted genetic studies in the early 1970s on retroviruses that infect chickens. Studies showed that virus contains a gene (designated *src* for sarcoma) that codes for a protein product. Product must be made in order for cell to become cancerous. San Francisco researchers Michael Bishop, far left, and Harold Varmus, near left, showed that *src*-like gene is present in normal cells of nearly all animals. Virus somehow picked up the gene from the cell. Ubiquity of *src*-like gene suggests it maintained an important function throughout evolution.

"When we compared the RNA of the (mutant) virus," Duesberg continues, "with the RNA of one that caused cancer, we found the RNA of the mutant was shortened. What was missing was a gene." Just how this gene works is under intense investigation. The fact that such genes are not unique to viruses, and that very similar genes have been found in many types of animal cells helps make this puzzle all the more interesting.

"We began wondering why some viruses have the *src* gene and others didn't," says Michael Bishop of the University of California, San Francisco. He and colleagues Harold Varmus and Dominique Stehelin knew that retroviruses could associate "intimately" with a cell's genes. "We suspected that the virus might have picked up some genetic information from the cell at one time or another," Bishop adds, pointing out that genetic information often is swapped from place to place along the gangling molecules of DNA in cells. A dormant virus whose genetic information was mixed in with a cell's could participate easily in the gene swapping process (known as recombination) and so pick up some extra genes or pieces of genes.

The search for the *src* gene has turned up some surprises. Instead of being a relatively rare gene, peculiar to these odd many scientists now agree that the process is of fundamental importance to living cells. Already scientists have exciting new information on the regulation of blood proteins — hemoglobin and immunoglobulin. The findings may be valuable in treating diseases of these blood proteins, such as thalassemia, as well as in understanding normal processes, such as how antibodies are made.

The discovery of split genes explained a notion that has long puzzled biologists: Animal cells contain much more DNA than they need to make the proteins necessary for life. The question that scientists are now asking is what is all the excess DNA doing in the cell? Does it have a role in evolution, in regulating normal cell processes, in cancer? Solutions await new discoveries in the next decade.



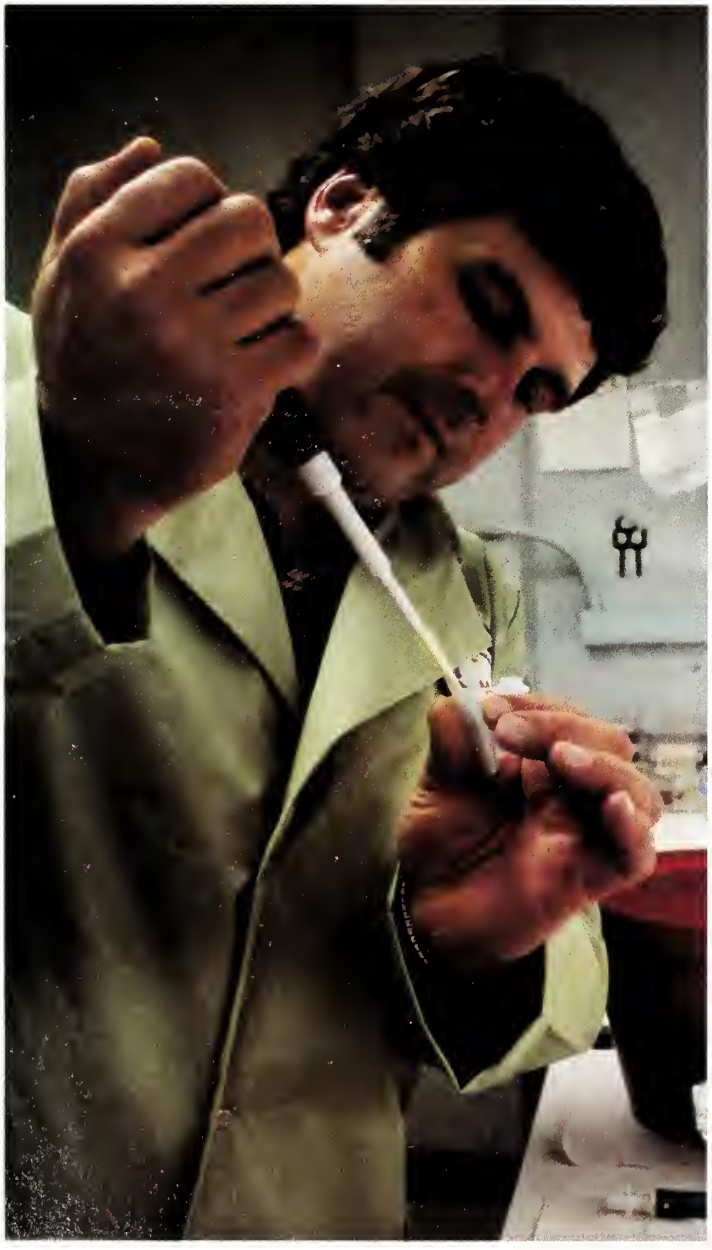
Dr. Phillip Sharp and students, left, do research in converted chocolate factory, now MIT's Center for Cancer Research. Sharp was among scientists who discovered in 1977 the unique way animal cells process DNA information into protein. Working with adenovirus, one that causes cancer in certain animals, Sharp showed gene for virus coat protein to be much longer than necessary. Diagram illustrates subsequent findings. Messenger RNA carries message from DNA in cell's nucleus to cytoplasm where protein is manufactured. Messenger RNA contains more information than needed to code for protein. Nonsense material, called "intervening sequences," is spliced out of messenger RNA by enzymes, much like process used in recording tapes. Functioning pieces are then joined together. New "trimmed" RNA specifies protein structure. Finding of intervening sequences implies flexibility — cell can alter protein to fit new situations. Gene coding for blood protein immunoglobulin can shuffle sequences to make different antibodies. Genes of bacteria occur in one piece. Discovery of split genes awaited scientists' ability to probe animal cells with cancer viruses.

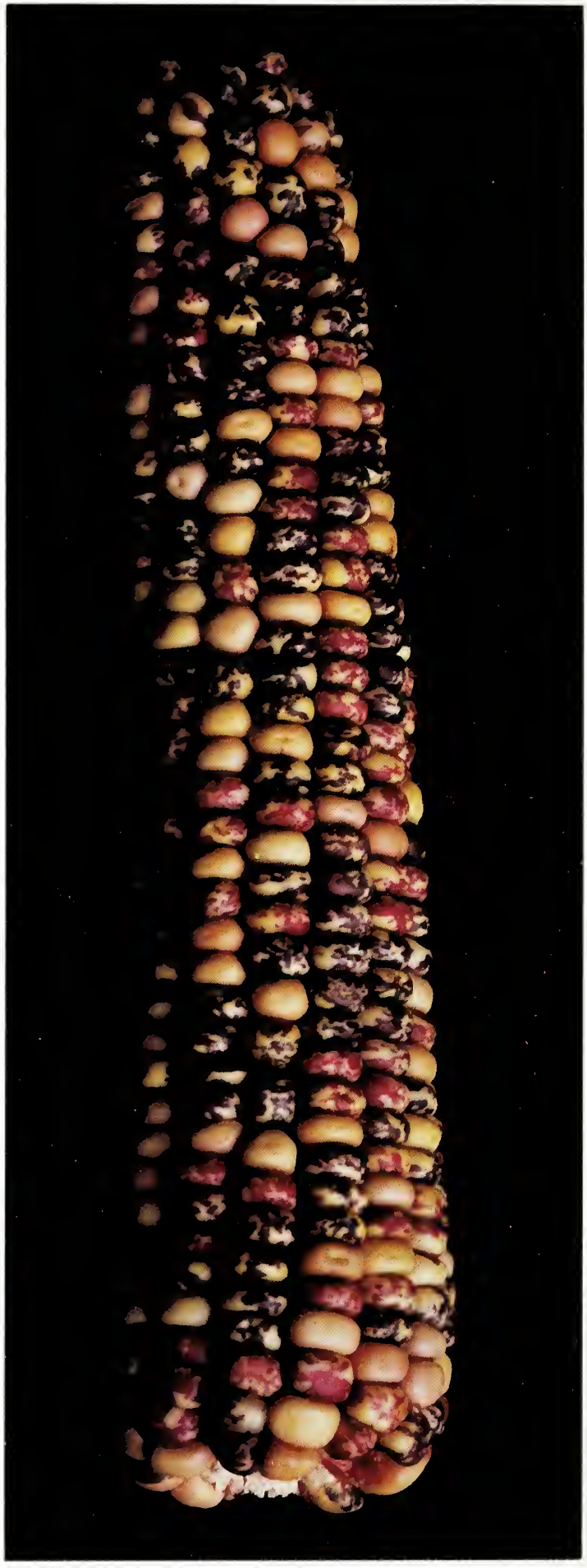
viruses, the *src* gene is all over the place. "We found it in normal cells of birds, mice — every animal cell we examined," Bishop says. "In fact, we even found a very similar gene in human cells.

"It isn't part of a virus in these cells, and it doesn't usually cause cancer," he continues. "it's a normal cellular gene."

Just how or why this normal gene sometimes acts highly abnormally has become a crucial question. One way scientists have of answering the question is to find out what instructions that gene carries and what product it makes. And scientists are using new methods to read the genetic code in the *src* gene to help answer such questions. Information now is being gathered rapidly.

Many genes carry the information that specifies the structures of proteins, and the *src* gene is no exception. "Making the tools that allowed us to isolate the *src* gene protein was difficult and frustrating," admits Raymond Erikson of the University of Colorado. But in 1977, he and his colleagues first identified that protein and soon realized that it is a particular type of enzyme. This, by itself, is not surprising. Cells have thousands of enzymes, and even the retroviruses have a few genes for making specialized proteins. What intrigued Erikson and his colleagues is that the *src* protein actually is a "protein kinase," an enzyme that can change yet other enzymes chemically, thereby affecting how





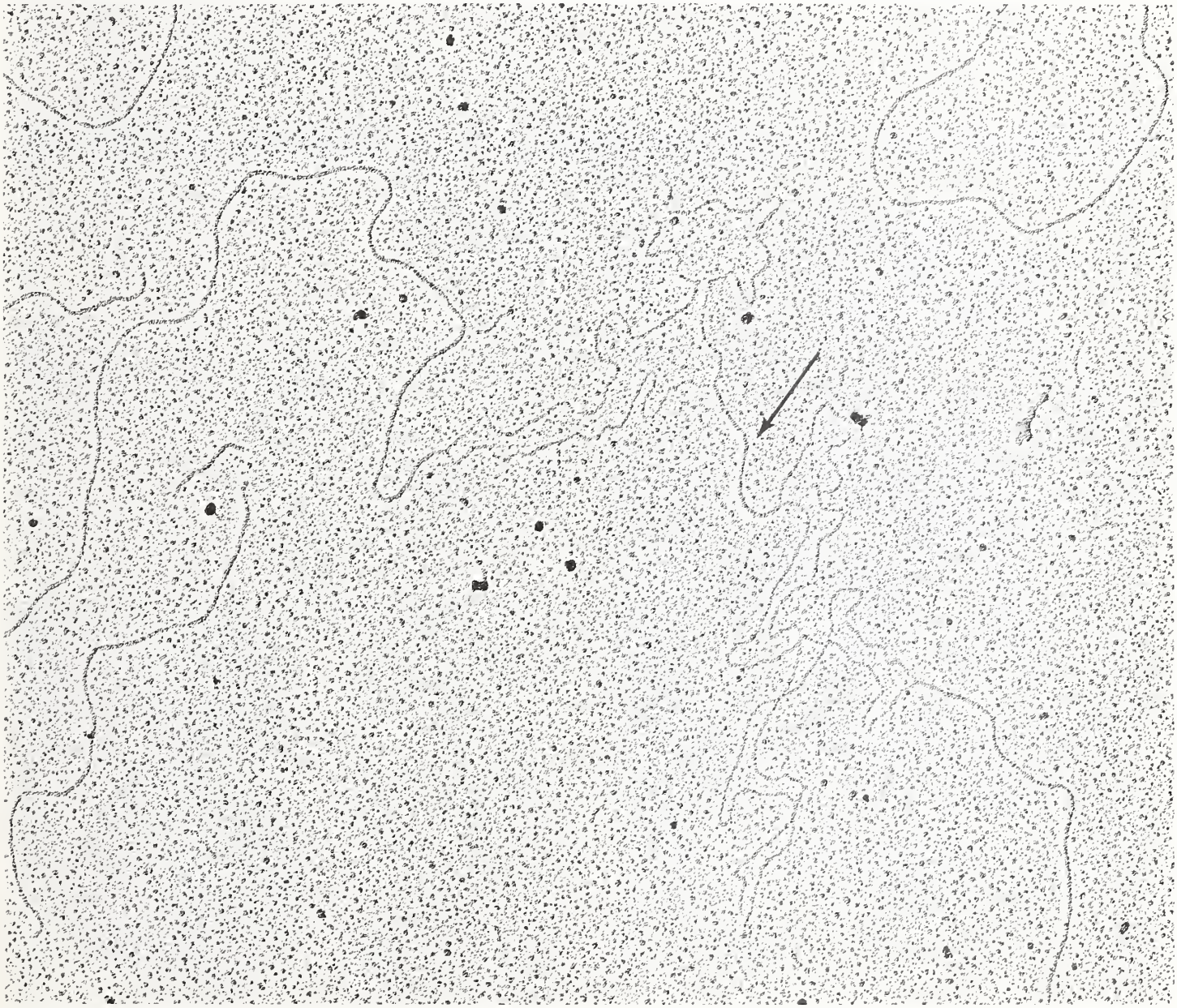
George Vande Woude, far left, of the National Cancer Institute, is studying the intricacies of the *src* gene with recombinant DNA techniques. Micrograph, below, shows how similar regions of DNA from mouse retrovirus and normal mouse cell stick together because they have stretches that carry same DNA code. Region contains gene acquired by virus from cell. Research by Vande Woude and others suggests that retroviruses have additional stretches of DNA that act as switches, turning on certain genes when inserted next to them in the cell's chromosome. Similar activation of genes caused variation in pigmentation of corn kernels. These activated genes are moveable; they can pop out of one chromosome and into another. Scientists call them jumping genes or transposons.

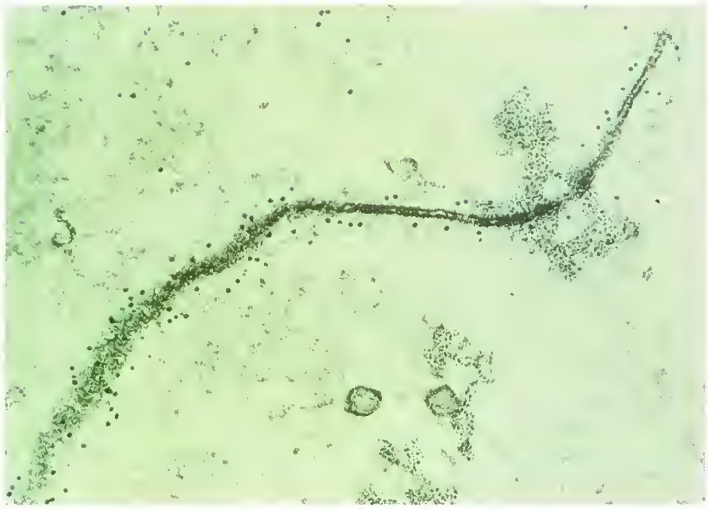
they function in cells.

No one yet is sure of just what enzymes in a cell are changed by the *src* protein. But here again, several meandering avenues of inquiry now may be converging. For instance, scientists know that many cellular activities can be controlled by kinase enzymes. The virus' kinase might be interfering with those delicate control mechanisms and so help to throw off orderly behavior of cells.

Also, the *src* protein seems to work at, or along the membrane of cells, that is, the outer skin or barrier that separates the cell from its environment. Many scientists have identified the membrane as a key cell entity that changes structure and behavior when a cell becomes cancerous. Says the National Cancer Institute's Ira Pastan, "While this does not really tell us what the *src* protein is doing, it gives us a clue. We know that cancer cells lose the ability to adhere, or stick to one another. We know that they change their shape — they round up and their edges ruffle." Thus, the virus' kinase might contribute to these important changes at a cell's surface, possibly by loosing a cascade of cell enzyme changes. Those changes, in turn, might alter drastically the cell's membrane, affecting how the cell grows and even how it outgrows its neighbors.

If the *src* protein from a retrovirus can trigger so many catastrophic events in a cell, what keeps the same thing from happening by means of the *src*-like protein already in most normal cells? Very little, it seems, says NCI's George Vande Woude. He has used copies of the *src* gene from a mouse virus, called the Moloney sarcoma virus, to look for and at the *src*-like gene in ordinary cells from a mouse. The normal mouse *src*-like gene,





***Src* protein associated with Rous virus is labeled with black iron particles in picture at left. Protein is found along the inner membrane of infected cells. Scientists know the protein is a kinase — an enzyme that reacts chemically to change other proteins. But they have yet to learn how *src* protein changes normal cells to cancer. The kinase may regulate one of the many proteins on cell's surface. Fibronectin is a protein glue that anchors cells and holds them to each other. Fluorescent-labeled fibronectin, right, is seen on surface of single cell (red) and on layer of cells (green). Fibronectin often disappears when cells become cancerous.**

taken by itself, won't change the ordinary healthy behavior of those mouse cells. But if a small bit of DNA taken from the virus is added onto the mouse cell's *src*-like gene, "it's as if this small bit had thrown the switch," Vande Woude exclaims. The mouse cells now become transformed by the *src*-like gene — that is, they grow uncontrolled like cancer cells.

The effect is remarkable, and it's reminiscent of curious but important findings from an altogether separate arena of research. The added on bit of DNA, that enables the *src*-like gene to exert its transforming effect on cells, resembles a transposon.

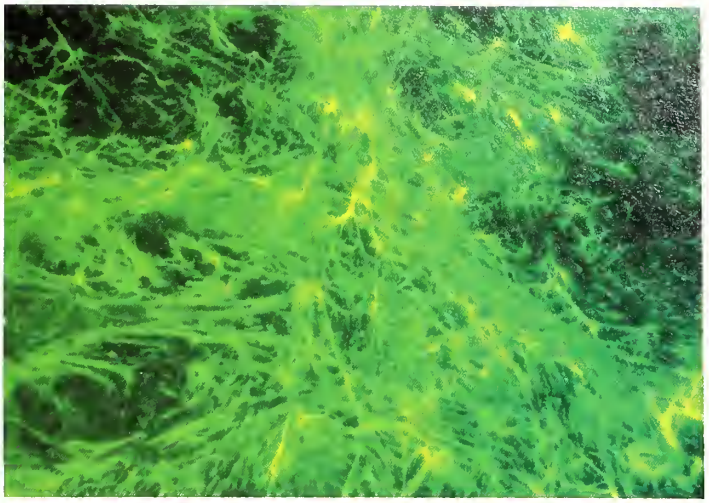
Transposons are jumping genes — stretches of DNA containing genes that can move about and into other much longer stretches of DNA. A certain arrangement of DNA subunits at either end of a transposon enables it to insert into and pop out of a cell's chromosome. The same arrangement of DNA subunits occurs in the small bit that causes the *src*-like gene to transform cells. Transposons were discovered in corn where they cause kernels to appear mottled. Barbara McClintock of the Cold Spring Harbor Laboratory made this observation in the 1940s. Much later transposons were found also in bacteria where they act like biological on-off switches.

Only recently have scientists realized that a small piece of virus

Hepatitis B Virus and Cancer

When Baruch Blumberg began his search for unique blood proteins, he did not expect to find a virus. But the discovery of a new particle in a serum sample from an Australian aborigine and later in a sample from a patient with hepatitis won him the Nobel prize in 1976. It also enabled Blumberg and colleague Irving Millman, both of the Institute for Cancer Research in Philadelphia, to develop a vaccine that successfully prevented the liver infection among homosexuals, who are at high risk of viral hepatitis and who agreed to participate in a clinical trial conducted in New York City. Several studies suggest that people whose blood contains hepatitis B virus are more likely to get liver cancer. There is hope that the vaccine eventually also might play a role in

Baruch Blumberg discovered particle in human blood associated with hepatitis B virus and helped develop vaccine against the liver infection. Areas where infection is common, far right, parallel those with high incidence of liver cancer. Peanuts, left, is a member of woodchuck colony at Philadelphia zoo. These woodchucks carry a hepatitis B-like virus in their blood and are being studied to understand link of virus to liver cancer.



is all that's needed to change a cell from normal to cancerous growth. No one fully understands how this happens or, equally important, what it means. Perhaps by inserting itself, the virus perturbs the cell's chromosome, possibly switching on an otherwise quiet gene to make too much of a particular protein at the wrong time. Whatever the eventual explanation, *src* genes undoubtedly are doing something in cancer cells they ought not to be doing.

Thus, the story of viruses once again seems to speak remarkably directly to the study of human cancer. In animal cells, such as those from mice, tumor viruses are able to commandeer cells by making seemingly fine adjustments to their genes. The same mode of action may describe how other cancer causing agents trigger a cell's change from orderly to cancer-like growth. Even if human cancer can happen totally without auxiliary help from virus genes, the recent lessons from the tumor causing viruses of animals have provided remarkable insight into the basic biology that takes place during malignant transformation.

preventing this form of cancer, which ranks as one of the most common causes of death from cancer worldwide.

The particle Blumberg discovered — called Australia antigen — is the protein coat of the hepatitis B virus. The complete virus particle was identified later. Australia antigen is detected by immunologic methods, such as radioimmunoassay. It is present in the blood of persons with active hepatitis and in those who are not sick but carry the virus in a dormant form. These individuals or carriers appear unable to mount an immune response to clear the virus from their bodies.

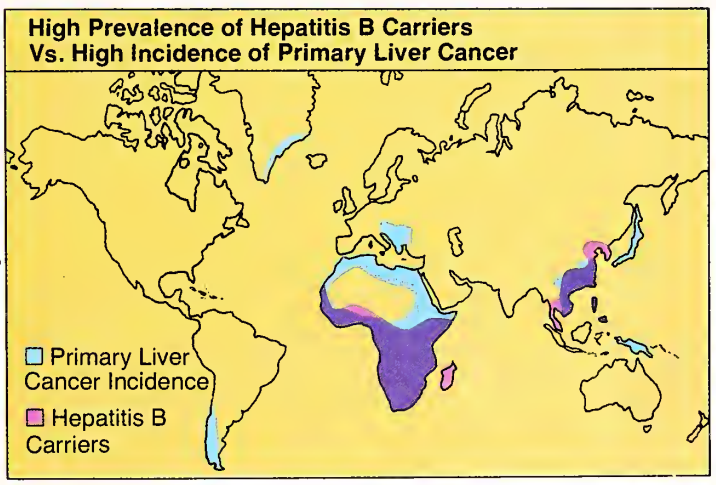
In addition to blood, hepatitis B virus has been found also in saliva, seminal fluid, and menstrual and vaginal discharges of infected individuals. It is usually transmitted through a break in the skin. In the United States a blood transfusion from an infected individual was a common way of transmission. The active infection usually lasts for several weeks, and about 5 to 10 percent of its victims develop chronic hepatitis with persistent liver damage.

Radioimmunoassays of blood samples collected around the world show that about 1 in 1000 people in the U.S. and Europe are carriers of the virus. But in parts of southeast Asia and South Africa, up to one in five people test positive for Australia antigen.

The thought that the virus might be associated with liver cancer arose when epidemiologists noted a similiar distribution worldwide for the incidence of primary liver cancer. (Many forms of cancer spread to the liver; this is secondary liver cancer and is not associated with hepatitis B virus infection.) When liver cancer patients were tested for the presence of Australia antigen in their blood, more than 80 percent of them were positive. Epidemiological studies conducted in various parts of the world strengthen the link. One of them is following 6,000 male government workers in Taiwan — half of whom are carriers. After 4 years, 43 of the workers developed liver cancer; all but one of the cases occurred in carriers of the virus.

An additional piece of evidence strengthening the link between hepatitis B virus and liver cancer is the discovery of a similar association in the animal kingdom. Philadelphia scientists Robert Snyder and Jesse Summers found a virus similar to the human one in 10 to 20 percent of woodchucks captured from fields in Pennsylvania and New Jersey. A colony of these woodchucks lives at the Philadelphia zoo. Here, free from predators, the woodchucks die of chronic diseases. Postmortem examinations conducted by Snyder over the past 18 years show about a quarter of the woodchucks die of liver cancer; they also have the virus in their blood samples.

No one is suggesting that the virus directly causes liver cancer. Rather, Blumberg and others think that virus infection might be one of several steps that lead to liver cancer years later. Persistent infection with hepatitis B damages liver cells — cirrhosis, for example, is common among carriers. Other factors, possibly in the environment, may push the already infected liver cell toward cancer. One suspected additional factor is aflatoxin, a product of fungus that grows on stored peanuts and grains. It is a potent liver carcinogen in animals. Aflatoxin too is more prevalent in areas of the world where liver cancer is common. Blumberg and others hope the hepatitis vaccine might prevent one event, the initial liver infection, and thereby break the chain of events leading to liver cancer.



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